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ANTI-TUBERCULOSIS drug RESISTANCE IN THE WORLD

THE WHO/IUATLD GLOBAL PROJECT ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

WORLD HEALTH ORGANIZATION

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The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance
1994 - 1997

WRITING COMMITTEE

- Ariel Pablos-Méndez, M.D., M.P.H., Global Tuberculosis Programme, WHO, Geneva, Switzerland; Divisions of General Medicine and Epidemiology, Columbia University, New York, NY, USA.
- Adalbert Laszlo, Ph.D., Laboratory Centre for Disease Control, Ottawa, Canada; International Union Against Tuberculosis and Lung Disease (IUATLD).
- Flavia Bustreo, M.D., M.P.H., Global Tuberculosis Programme, WHO, Geneva, Switzerland.
- Nancy Binkin, M.D., M.P.H., Division of TB Elimination, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA.
- David L. Cohn, M.D., Denver Disease Control Service, Denver, CO, USA.
- Catherina S.B. Lambregts-van Weezenbeek, M.D., Royal Netherlands Tuberculosis Association (KNCV), The Hague, The Netherlands.
- Sang Jae Kim, Sc.D., Korean Institute of Tuberculosis, Seoul, Republic of Korea; WHO-WPRO, Manila, Philippines.
- Pierre Chaulet, M.D., Global Tuberculosis Programme, WHO, Geneva, Switzerland.
- Paul Nunn, M.D., Global Tuberculosis Programme, WHO, Geneva, Switzerland.
- Mario C. Raviglione, M.D., Global Tuberculosis Programme, WHO, Geneva, Switzerland.

GLOBAL NETWORK OF SUPRANATIONAL REFERENCE LABORATORIES

Dr Adalbert Laszlo, *Canada (Coordinating Center)*
Dr Chyoji Abe, *Japan*
Dr Masakazu Aoki, *Japan*
Dr Jack Crawford, *United States of America*
Dr Fadila Boulahbal, *Algeria*
Dr Gisela Bretzel, *Germany*
Dr David Dawson, *Australia*
Dr Isabel de Kantor, *Argentina*
Dr Francis Drobniewski, *UK*
Prof. Knut Feldmann, *Germany*
Dr Sven Hoffner, *Sweden*
Dr N.K. Jain, *India*
Dr Gunilla Källenius, *Sweden*
Dr Sang Jae Kim, *Korea*
Dr Nuria Martin-Casabona, *Spain*
Dr Maria Fernanda Pereira, *Portugal*
Prof. Francoise Portaëls, *Belgium*
Dr Sabine Rüsch-Gerdes, *Germany*
Mr Ronald Smithwick, *United States*
Prof. V. Sticht-Groh, *Germany*
Prof. Richard Urbanczik, *Germany*
Dr Bert van Klingeren, *The Netherlands*
Dr Vérinique Vincent, *France*
Dr Karin Weyer, *South Africa*

CONTRIBUTING MEMBERS OF THE WORKING GROUP

Argentina: Dr Lucy Barrera, Dr Omar Latini; **Australia:** Dr David Dawson; **Benin:** Dr Martin Gninafon, Dr Séverin Anagonou, Dr Arnaud Trébucq; **Bolivia:** Dr Marcia Ferrel Urquidi, Dr Mirta Camacho; **Botswana:** Dr Michael Masekawa, Dr Thomas Kenyon; **Brazil:** Dr Angela Werneck Barreto, Dr J. Ueleres Braga, Dr Miguel Aiub Hijjar; **China (Henan province):** Dr Wang Guobin, Dr Cheng Shao Ji; **Cuba:** Prof. Jose A. Valdivia, Dr Ernesto Montoro, Dr Antonio Marrero Figueroa; **Czech Republic:** Dr Marta Havelková, Dr Milan Kubin, Prof. O. Ostádal; **Dominican Republic:** Dr Marcos Espinal; **Estonia:** Dr Annika Kruuner; **France:** Prof. Jacques Grosset, Dr Valérie Schwoebel, Prof Bernard Carbonnelle; **India (Delhi state):** Dr N.K. Jain; **Italy:** Prof. Gioacchino Angarano, Dr Sergio Carbonara; **Ivory Coast:** Dr Malick Issa Coulibaly, Dr Mireille Dosso, Dr Arnaud Trébucq; **Kenya:** Dr W.A. Githui; **Latvia:** Dr Richard Zalesky, Dr Charles Wells, Dr A. Karklina, Mr Ronald Smithwick; **Lesotho:** Dr Brenda Corcoran; **Nepal:** Dr Dirgha Singh Bam, Dr Ian Smith, Dr Pushpa Malla; **Netherlands:** Dr Bert van Klingeren, Dr Catherina S.B. Lambregts-van Weezenbeek; **New Zealand:** Dr Maggie Brett; **Peru:** Dr Jaime Portocarrero Céliz, Dr Pedro G. Suarez, Ms Lucy Vàsquez Campos; **Portugal:** Dr Maria L. Antunes, Dr Maria Filomena Rodrigues, Dr Maria F. Pereira; **Puerto Rico:** Dr Olga Joglar; **Republic of Korea:** Dr Sang Jae Kim; **Romania:** Prof. E. Corlan; **Russian Federation (Ivanovo Oblast):** Prof. Alexander G. Khomenko, Prof V.I. Golyshevskaya; **Sierra Leone:** Dr Lars Weitman, Dr Abu G. George; **Spain (Barcelona):** Dr Nuria Martin-Casabona; **Swaziland:** Dr Richard Lemmer; **Thailand:** Dr Vallop Payanandana, Ms Dhanida Rienthong; **United Kingdom:** Dr John Watson, Dr Francis Drobniewski, Dr Elizabeth Mitchell, Dr Peter Christie; **USA:** Dr Eugene McCray, Dr Ida Onorato, Dr Nancy Binkin; **Vietnam:** Dr Le Ngoc Van, Dr N.D. Huong, Dr Nguyen Thi Ngoc Lan, Prof Nguyen Viet Co; **Zimbabwe:** Dr Jacob van der Have

OTHER MEMBERS OF THE WORKING GROUP

Chile: Dr Pedro Valenzuela; **China (Shandong province):** Dr Cheng Shao Ji; **Guinée:** Dr Oumou Bah-Sow; **Guinea Bissau:** Mrs Tuija Koivula; **Hong Kong;** Dr Kai Man Kam; **India:** Dr C.N. Paramasivan, Dr S.P. Khanna, Dr D.R. Nagpaul; **Iran:** Dr Mohammad-Reza Masjedi; **Italy:** Dr Giovanni B. Migliori, Dr Antonio Cassone, Dr Graziella Orefici; **Malaysia:** Dr I. Kuppusamy, Dr Padmini Denis, Ms R. Soshila; **Mexico:** Dr Adalberto Santaella-Solis, Dr Susana Balandrano, Dr Reuben Granich, Dr Jordan Tappero; **Nicaragua:** Dr Jose Ramon Cruz**,** Dr Luis Chacon; **Poland:** Prof. Kazimierz Roszkowski, Prof. Zofia Zwolska; **Singapore:** Dr Jane Yap; **Tanzania:** Mr T.M. Chonde, Dr Y.A. Ipuge; **Uganda:** Dr Francis Adatu, Dr M.A. Azziz, Dr Thomas Aisu; **Other:** Dr Eric Brenner (*USA*), Dr Michael Felten (*Germany*)

THE SECRETARIAT OF WHO

Dr A. Kochi, GTB
Dr P. Nunn, GTB/TRS
Dr S. Spinaci, GTB/NPS
Dr M.C. Raviglione, GTB/TRS
Dr A. Pablos-Méndez, GTB/TRS
Dr F. Bustreo, GTB/TRS
Prof. P. Chaulet, GTB/NPS
Dr F. Luelmo, GTB/NPS
Dr E. Netto, GTB/TRS
Dr C. Dye, GTB/TRS
Dr D. I. Ahn, WPRO
D. L. Blanc, WPRO
Dr R. Rodriguez Cruz, PAHO/AMRO
Mrs D. Weil, PAHO/AMRO
Dr E. Nyarko, AFRO
Dr Z. Hallaj, EMRO
Dr A. Seita, EMRO
Dr T.A. Madaras, EURO
Dr M.V. H. Gunaratne, SEARO

THE SECRETARIAT OF THE IUATLD

Dr N. Billo
Prof. D. Enarson
Prof. J. Murray
Dr H.L. Rieder
Dr A. Trébucq

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FOREWORD

Bleeding, purging, bed rest, horseback riding, the mountains, the seashore, cod-liver oil, castor oil, chalmoogra oil, phrenic nerve interruption, thoracoplasty, pneumothorax, lucite ball or paraffin plombage, air in the chest, air in the abdomen ... the list of attempted remedies from the Greeks to the moderns seems nearly infinite. The length of the roster is a powerful testimony to the lack of efficacy of any of these measures.

However, in the eight years from 1944 to 1952, three substances were uncovered which finally proffered predictable curative therapy for "consumption". Guided by the observation that various species of soil organisms could establish a local hegemony, presumably by releasing substances that inhibited other similar microbes, Waksman initiated a laboratory at Rutgers University to test for "antibiotic" activity among these microbes. Schatz, a Ph.D. candidate in the laboratory, came upon just such an organism in 1943, one recovered from a nearby chicken coup. Eventually named *Streptomyces griseus*, these microbes elaborated a substance, "streptomycin", which was potently inhibitory for tubercle bacilli.

Almost simultaneously in Europe, the para-amino salt of salicylic acid (PAS) had been synthesised, inspired by the brilliant intuition of Lehman that such a compound should interfere with essential metabolism of *Mycobacterium tuberculosis*.

Pressed into clinical use after minimal human safety testing, both streptomycin and PAS were found to be of clear and demonstrable efficacy in the treatment of tuberculosis. However, in only a few years, it became apparent that using these agents singly led to treatment failure and acquired drug resistance among substantial numbers of persons under therapy. The British Medical Research Council, led by Phillip D'Arcy Hart, then conducted an original type of investigation in which they compared in a randomised format, the efficacy of these drugs singly and together. The data clearly showed the advantage of combined treatment in reducing acquired drug resistance and failures.

The combination of PAS and streptomycin, while better, still fell short of the Holy Grail of prompt, predictable, and universal cures. However, the missing link to this process was to be discovered in 1952. Domagk, a field corpsman in the first world war, had watched many young soldiers die from the infectious complications of relatively trivial wounds. Determined to help prevent such tragedies in the future, he embarked on a remarkably tenacious series of studies in the 1920's, 30's, and 40's to find effective agents to combat such infections. His synthesis of "prontosil rubrum", a pro-drug for the "sulfa" antimicrobial agents, earned him the Nobel Prize in medicine in 1938. Driven by the knowledge that wars had always spawned epidemics of tuberculosis, Domagk continued his work with a series of compounds seeking agents with greater activity against tuberculosis. In 1951-52, three groups—including Domagk's—had come upon isonicotinic acid hydrazide (INH)—then and now the most potent single anti-tuberculosis agent.

Triple therapy—INH, PAS, and streptomycin—would cure nearly all tuberculosis patients save those who arrived too near passage through Death's Door. However, as the product of the perverse, imperfect nature of humankind and the resilient adaptability of the tubercle bacillus, inadequate treatment still continued to breed drug-resistant strains of the tubercle bacillus.

Although vexing and potentially lethal for individual patients, these drug-resistant strains seemed destined to occupy a relatively small portion of the spectrum of disease in any given community, state or nation. Laboratory and epidemiological data broadly hinted that INH resistant and multidrug-resistant (MDR) strains were of lessened virulence, putting them at a relative ecological disadvantage.

This scenario was dramatically challenged as a third organism, the human immunodeficiency virus (HIV), was introduced into the ecosystem. HIV, by compromising human immunity, facilitated the rapid spread of tuberculosis including MDR-TB strains through large populations. While much of the MDR-TB morbidity and mortality was found among those HIV infected, there was clear evidence of horizontal spread of such infections to the general community. Thus, as we near the next millennium with tuberculosis still endemic throughout much of the world and HIV making rapid inroads into these same populations, the relative importance of drug-resistant tuberculosis would seem to soar. Sadly, in the regions of the world where these co-pathogens are most pervasive, poverty and sorely limited public health laboratory services have obscured the extent of drug resistance.

Thus, the urgent and compelling need for this study. As noted by the authors and participants, this is not a "perfect" study. But it is an admirable, laudable, and highly useful document which will establish regional patterns to serve as benchmarks for future trends, to provide guidelines to help select appropriate chemotherapy regimens, and to inform interested agencies or institutions of the need for specialised treatment facilities, means to halt community or institutional transmission of tuberculosis, new drugs, and vaccines. As such, this is a sentinel project for which the investigators and participants should be congratulated.

Dr Michael Iseman
National Jewish Medical and Research Center
Denver, Co, USA

SUMMARY

BACKGROUND

Antimicrobial resistance in previously susceptible organisms occurs wherever antibiotics are used for the treatment of infectious diseases in humans and animals. With increasing antibiotic use, and misuse, over the past decades, resistance has emerged in all kinds of micro-organisms — including *M. tuberculosis* — posing new challenges for both clinical management and control programmes.

Resistance of *M. tuberculosis* to antibiotics is a man-made amplification of spontaneous mutations in the genes of the tubercle bacilli. Treatment with a single drug — due to irregular drug supply, inappropriate prescription, or poor adherence to treatment — suppresses the growth of susceptible strains to that drug but permits the multiplication of drug-resistant strains. This phenomenon is called *acquired resistance*. Subsequent transmission of such resistant strains from an infectious case to other persons leads to disease which is drug-resistant from the outset, a phenomenon known as *primary resistance*.

Dramatic outbreaks of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected patients in the United States and in Europe have recently focused international attention on the emergence of strains of *M. tuberculosis* resistant to antimycobacterial drugs. MDR-TB — defined as resistance to the two most important drugs, isoniazid (INH) and rifampicin (RMP) — is a potential threat to tuberculosis control. Patients infected with strains resistant to multiple drugs are extremely difficult to cure, and the necessary treatment is much more toxic and expensive.

Drug resistance is therefore a potential threat to the standard international method of TB control: the DOTS strategy ("Directly Observed Treatment, Short-course"). In 1994, WHO embarked on the project presented in this book to discover the extent of that threat. At that time, the available information suggested that levels of resistance may have been increasing in some settings, but methodological limitations prevented an

adequate assessment of the extent of the problem throughout the world and precluded meaningful comparisons between different countries.

WHO/IUATLD GLOBAL PROJECT ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

In early 1994, the WHO's Global Tuberculosis Programme joined forces with the International Union Against Tuberculosis and Lung Disease (IUATLD) and started the Global Project on Anti-tuberculosis Drug Resistance Surveillance. The objectives of the project were to measure the prevalence of anti-tuberculosis drug resistance in several countries world-wide using standard methods and to study the correlation between the level of drug resistance and treatment policies in those countries.

The first step towards achieving the objectives was the development of common definitions and guidelines by world experts in 1994. These focused around three major principles: 1) surveillance must be based on a sample of TB patients representative of all cases in the country; 2) primary and acquired drug resistance must be clearly distinguished in order to interpret the data correctly; and 3) proper laboratory performance must be assured.

The second step was the establishment of a Global Network of Supranational Reference Laboratories (SRLs) to serve as the reference centres for quality assurance of drug-susceptibility testing (DST). Currently, the network comprises 22 SRLs. The third step was to organise a Working Group under the leadership of WHO with representatives of national tuberculosis programmes (NTPs) and research institutions from over 50 countries to implement surveillance projects at country level.

The First Phase of the Global Project described in this report includes results from 35 countries in five continents. Surveillance or surveys were conducted on approximately 50,000 tuberculosis cases sampled from areas representing 20% of the world's population. Each study enrolled 59 to 14,344 TB patients (mean 1,200). Testing for INH and RMP was accurate; resistance to ethambutol (EMB) and streptomycin (SM) was also evaluated. Overall agreement between the SRL and the various National Reference Laboratories was 96%. All countries, except three, distinguished between primary and acquired resistance.

MAIN FINDINGS

Primary drug resistance. This information is obtained from cases with effectively no previous treatment. It reflects the transmission of strains that were already resistant. The prevalence of resistance to any drug ranged from 2% (Czech Republic) to 41% (Dominican Republic), with a median value of 10.4%. Primary resistance to all 4 drugs tested was found in a median of 0.2% of the cases (range 0 to 4.6%). Primary MDR-TB was found in every country surveyed except Kenya, with a median prevalence of 1.4%, range 0 (Kenya) to 14.4% (Latvia).

Acquired drug resistance reflects more recent case mismanagement. The populations assessed for this are patients who have been treated for a month or longer in the past. As expected, the prevalence of acquired drug resistance was much higher than that of primary drug resistance. The prevalence of acquired resistance to any drug

ranged from 5.3% (New Zealand) to 100% (Ivanovo Oblast, Russia), with a median value of 36%. Resistance to all 4 drugs among previously treated patients was reported in a median of 4.4% of the cases (range 0 to 17%). The median prevalence of acquired MDR-TB was 13%, with a range of 0% (Kenya) to 54% (Latvia).

Overview of the global situation. These findings are probably an underestimate of the magnitude of the problem worldwide as the countries surveyed had better TB control than average. Resistance to tuberculosis drugs is probably present everywhere in the world. Certainly, MDR-TB is present in five continents, a third of the countries surveyed having levels above 2% among new patients. In Latvia 30% of all patients presenting for treatment had MDR-TB. The region of Russia surveyed had 5% of TB patients with MDR-TB. In the Dominican Republic, 10% of TB patients had MDR-TB. In Africa, Ivory Coast has also witnessed the emergence of MDR-TB. Preliminary reports from Asia (India and China) show high levels of drug resistance as well. In the State of Delhi, India, 13% of all TB patients had MDR-TB.

Correlation of prevalence of drug resistance with TB control policy and activities. An important finding of the study was the higher prevalence of MDR-TB in countries categorised by WHO as having poor control programmes. Similarly, the higher the proportion of retreatment cases (the result of a poor programme) and the higher the incidence of TB among children (an indicator of high TB transmission in recent years), the higher the levels of drug resistance. The use of standardised short-course chemotherapy regimens, on the other hand, was associated with lower levels of drug resistance.

CONCLUSIONS

1. Drug resistance is ubiquitous. The Global Project found it in all countries surveyed. The levels of resistance to INH are high, and continued failure to improve TB control will fuel multidrug resistance.
2. There are several "hot spots" around the world where MDR-TB prevalence is high and could threaten control programmes. They include Latvia, Estonia and Russia in the former USSR, the Dominican Republic and Argentina in the Americas, and Ivory Coast in Africa. Preliminary reports from Asia also show high levels of MDR-TB. Urgent intervention is needed in these areas.
3. There is a strong correlation between both the overall quality of TB control and use of standardised short course chemotherapy and low levels of drug resistance. A high prevalence of MDR-TB is the result of therapeutic anarchy. Half the countries or regions with the worst TB control had primary MDR levels above 2% , compared with one-fifth of those with moderate control, and none of the countries with the highest standard of TB control.
4. The MDR-TB level is a useful indicator of NTP performance. As shown by the Global Project and by previous experiences in Korea and New York, the prevalence of primary MDR-TB is a good "summary" indicator of the performance of NTPs in recent years.

RECOMMENDATIONS

A) Surveillance

For the future, the authors propose the following recommendations concerning surveillance:

1. The well established network of SRLs is a model for standardised surveillance of drug resistance and should be maintained as a global resource. Surveys using the SRL network need to be repeated in the same 35 countries around the year 2000 to determine MDR-TB trends over time.
2. Adequate assessment of the level of MDR-TB in large countries (China, India, Russia) requires expansion of surveillance activities beyond the regions studied. Areas not adequately covered during the first phase of the Global Project must be targeted.
3. Future surveys should collect and analyze individual data on age, HIV co-infection, and country of birth, and on the contribution of the private sector to drug resistance.

B) Management

1. Countries without the DOTS TB control strategy need to implement it. This is supported by the Global Project's finding of an association of low resistance and high quality TB control. Previous experience has also demonstrated falls in resistance, and even in MDR-TB, following the introduction of DOTS.
2. The Global Project did not directly address the issue of treatment regimens. Based on previous experience, however, no alterations to the first line treatment regimens recommended by WHO and IUATLD are yet required. For the management of drug-resistant TB, including MDR-TB, the reader is referred to "Guidelines for the Management of Drug-resistant Tuberculosis" (WHO/TB/96.210).

C) Research

1. The authors recommend research to:
   a) Assess the transmissibility and clinical virulence of MDR-TB compared to disease caused by drug-susceptible strains.
   b) To define the impact of MDR-TB on treatment outcomes under programme conditions in developing countries.
2. Pharmaceutical companies are urged to develop new anti-TB drugs. The prime need for such drugs is to make DOTS more efficient and to shorten the duration of treatment thus making resistance less likely to emerge.

CHAPTER ONE

INTRODUCTION

1.1 THE EMERGENCE OF DRUG RESISTANCE

Antimicrobial resistance in previously susceptible organisms occurs as antimicrobials are used for the treatment of infectious diseases in humans and animals. Although soil bacteria normally produce small amounts of antibiotics, our ecosystem has very recently been inundated with tons of man-made antibiotics, creating a sudden, unprecedented evolutionary stress on all susceptible micro-organisms. The natural selection of drug-resistant strains has created a virtual arms race between our technology and microbial evolution. With increasing antimicrobial use and misuse over the past several years, resistance to antimicrobial agents has emerged in viruses, bacteria, fungi and protozoa, posing new challenges for both clinical management and control programmes[1].

Dramatic outbreaks of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected patients in the United States[2,3,4,5,6,7,8,9] and in Europe[10,11,12,13] have recently focused international attention on the emergence of strains of *Mycobacterium tuberculosis* which are resistant to antimycobacterial agents. These outbreaks, occurring mainly in nosocomial settings, were associated with high-case fatality rates[8,9]. However, resistance of the tubercle bacilli to antimycobacterial agents was recognised soon after the introduction of effective chemotherapy[14,15,16], and it is not limited to immunocompromised patients[14,15,16,17]. While many surveys report drug-resistant tuberculosis around the globe, accurate and comprehensive data are few.

Drug-resistant tuberculosis is a significant threat to tuberculosis control because only a few effective drugs are available against *M. tuberculosis*[18]. In particular, the spread of strains resistant to the two most important drugs, isoniazid (INH) and rifampicin (RMP), could have serious repercussions on the epidemiology and control of tuberculosis. Not only are patients infected with strains resistant to multiple drugs less likely to be cured, but second- or third-line treatment is much more toxic and expensive than treatment of patients with susceptible organisms. In one study in the USA, treatment failed in 35% of

171 HIV-negative patients with MDR-TB despite the use of multidrug regimens individually tailored by an experienced team[19]. The cost of treating a case of MDR-TB in the United States was estimated at $180,000[20].

1.2 MECHANISMS OF AND FACTORS ASSOCIATED WITH ANTI-TUBERCULOSIS DRUG RESISTANCE

Resistance of *M. tuberculosis* to anti-tuberculosis drugs is a man-made amplification of a natural phenomenon. Unlike the situation in many bacteria, with *M. tuberculosis* there is no indication of horizontal gene transfer (acquisition of resistance plasmids or transposons). Wild strains of *M. tuberculosis* that have never been exposed to anti-tuberculosis drugs are almost never resistant, though natural resistance to specific drugs has been documented for *M. bovis* (pyrazinamide or PZA). However, for the purpose of drug resistance surveillance, the interest focuses on the random process of genetic mutations that lead to the emergence of clinical resistance to anti-tuberculosis treatment.

During bacterial multiplication, resistance to anti-tuberculosis drugs develops spontaneously and with a defined frequency (Table 1). Genetic mutations resulting in resistance of *M. tuberculosis* to RMP occur at a rate of 10^{-10} per cell division and lead to an estimated prevalence of 1 in 10^8 bacilli in drug-free environments; the rate for INH is approximately 10^{-7} to 10^{-9}, resulting in resistance in 1 out of 10^6 bacilli[21]. Bacillary populations larger than 10^7 are common in cavities[15]. Thus, *genetic resistance* occurs in the absence of antimicrobial exposure, but is diluted by the majority of drug-susceptible micro-organisms. The presence of antimicrobials provides the selective pressure for resistant organisms to become predominant, especially in patients with a large load of bacilli, e.g. those with extensive cavitary disease[22,23].

Exposure to a single drug — due to irregular drug supply, inappropriate prescription or poor adherence to treatment — suppresses the growth of susceptible bacilli to that drug but permits the multiplication of drug-resistant organisms[24,25]. This phenomenon is called *acquired resistance*. Subsequent transmission of such bacilli to other persons may lead to disease which is drug-resistant from the outset, a phenomenon known as *primary resistance* (Fig. 1). Every active drug against *M. tuberculosis* is bound to induce resistance, and the more active a drug is the more likely it is to induce clinical resistance[15].

Multiple drug resistance due to spontaneously occurring mutations is virtually impossible, since there is no single gene involved in MDR and mutations resulting in resistance to various drugs arise independently. For example, the likelihood of spontaneous mutations resulting in resistance to both INH and RMP is the product of the individual probabilities, i.e., 1 in 10^{14} (10^6x10^8)[26]. This is in fact the rationale for multidrug regimens in the treatment of tuberculosis[27,28]. However, in a bacterial population with baseline resistance to INH, spontaneous mutation may result in resistance to RMP in some bacilli. In such situations, treatment with INH and RMP will select strains resistant to both antimicrobials. A similar sequence of events may lead to resistance to other drug combinations, and eventually to all first-line anti-tuberculosis medications[8,19,29].

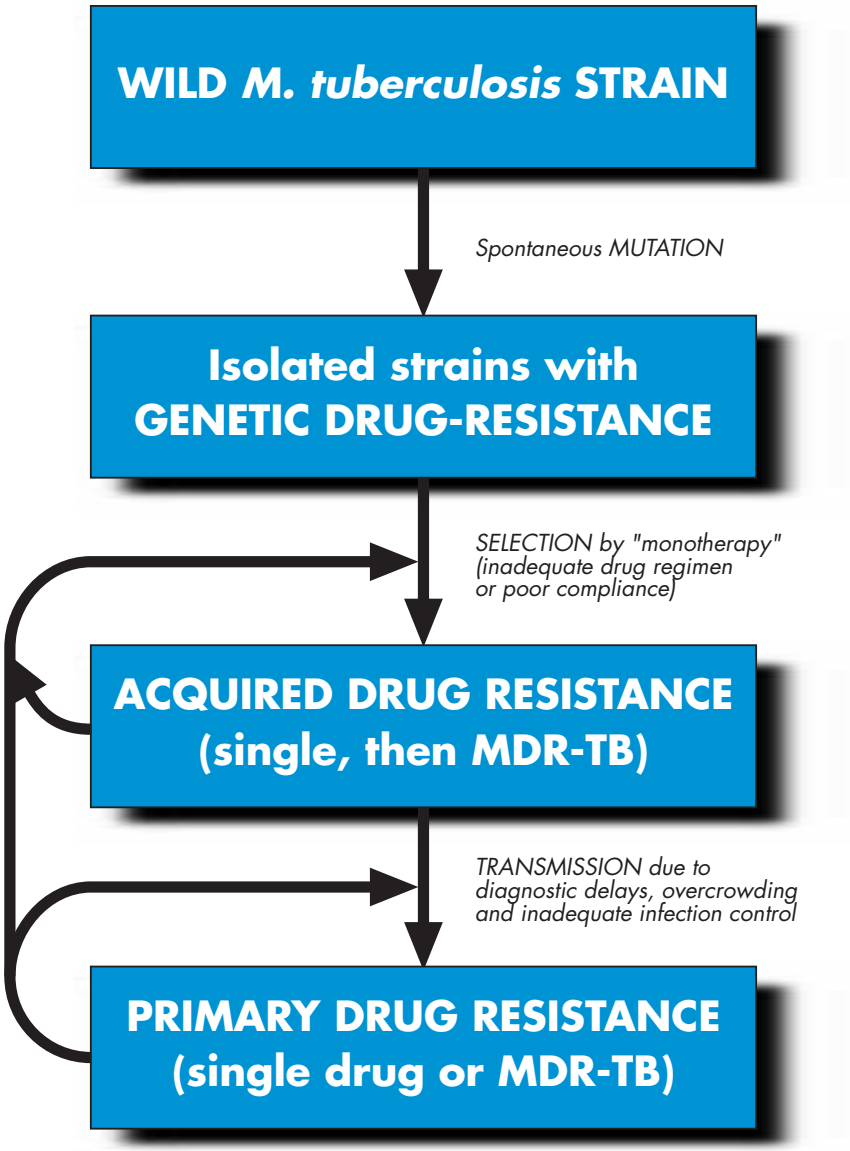
Table 1. Characteristics of the main anti-tuberculosis drugs

	Year of Introduction	Anti-tuberculosis Activity	BL/MIC*	Molecular target	Gene(s) involved in drug resistance	Mutation rate**	Wild-type resistance	Route of administration	Toxicity	Cost
FIRST-LINE DRUGS										
Isoniazid (INH)	1952	++++	100	Mycolic acid synthesis	*inhA* *kat*6	10^{-8}	1 in 10^{6}	oral	Low	Low
Rifampicin (RMP)	1965	++++	100	RNA poly-merase (ß-subunit)	*rpoB*	10^{-10}	1 in 10^{8}	oral	Low	Medium
Pyrazinamide (PZA)	1970	+++	5 to 10	?	*pnc*A	10^{-3}	1 in 10^{6}	oral	Low	Medium
Streptomycin (SM)	1944	+++	30	Ribosomal proteins	*rpo*L, *rrs*, *str*A, *S*12	10^{-8}	1 in 10^{7}	intramuscular	Medium	High
Ethambutol (EMB)	1968	++	3 to 4	Cell wall poly-saccharides	*emb* A,B & C	10^{-7}	1 in 10^{5}	oral	Low	Medium
SECOND-LINE DRUGS										
Ethionamide	1966	+++	5		?	10^{-3}	?	oral	High	Medium
Kanamycin/Amikacin	1957	+++	30	Ribosomal proteins	?	10^{-6}	?	intramuscular	Medium	High
Cycloserine	1955	++	3 to 4	Cell wall synthesis	?	10^{-10}	?	oral	High	High
Capreomycin	1967	++	5 to 10		?	10^{-3}	?	intramuscular	Medium	High
Thioacetazone	1950	+	10		?	10^{-3}	?	oral	Medium	Low
P-aminosalicylic acid (PAS)	1946	+	100	Folate biosynthesis	?	10^{-8}	?	oral	Medium	High
Ofloxacin	1987	++		DNA gyrase	*gyr* A & B	?	?	oral	Low	High

* BL/MIC: Ratio of blood levels to the minimum inhibitory concentration.

** Rate of mutation per cell division at the the gene(s) responsible for drug resistance.

Fig. 1. The development and spread of drug- and multidrug-resistant tuberculosis



The emergence of drug-resistant *M. tuberculosis* in a population has been associated with a variety of programmatic, health provider and patient-related factors[30]. In many countries, programme factors may include the lack of a standardised therapeutic regimen, or poor implementation compounded by frequent or prolonged shortages of drug supply in areas with inadequate resources or political instability. Use of anti-tuberculosis drugs of unproven quality is an additional concern, as is the sale of these medications over the counter and on the black market.

The development of drug resistance may involve departures by providers from the correct management of individual cases. Problems occur in selecting the appropriate chemotherapy regimen, sometimes due to lack of recognition of prior treatment, ignorance of the importance of standardised regimens, and errors such as addition of a single drug to a failing regimen[19,20]. In addition, providers may not monitor patients appropriately while on therapy. Finally, patients' nonadherence to prescribed treatment also contributes to the development of drug resistance[31,32,33,34]. Nonadherence is difficult to predict from demographic or social characteristics but is also less likely to occur in programmes with directly observed therapy (DOT)[35]. Another patient factor that has been associated with MDR-TB is HIV infection[36], although the results of studies in different countries have been inconsistent.

In the end, the crucial element in the emergence of drug resistance is not the patient or even the practitioner, but the lack of a properly organised system to ensure prompt diagnosis, effective treatment, and ongoing surveillance of tuberculosis[37]. For this reason, the level of anti-tuberculosis drug resistance in a population are an indicator of the National Tuberculosis Programme (NTP).

1.3 DRUG SUSCEPTIBILITY TESTING IN TUBERCULOSIS: A HISTORICAL PERSPECTIVE

International standardisation of drug susceptibility testing (DST) is needed for comparative evaluation of controlled chemotherapeutic trials, for epidemiological surveys on the prevalence of drug resistance, and for guidance in the treatment of tuberculosis patients[38]. Although WHO recommendations were developed for DST in general, they particularly apply to *M. tuberculosis* because these tests have been difficult to standardise. Factors influencing the tests and their interpretation include the potency and stability of the drugs, and the use of the proper bacterial inocula, drug concentrations, and resistance criteria. Moreover, standardised methods need to be proficiency-tested regularly in order to maintain reliable diagnosis of drug-resistant tuberculosis.

The lack of uniformity and reproducibility of the procedures for testing antimycobacterials was recognised soon after the introduction of tuberculosis chemotherapy. In 1955, Canetti[39] pointed out that the methods recommended for determination of INH resistance by the International Union Against Tuberculosis (IUAT), the Veterans Administration, the British Medical Research Council (MRC) and the US Public Health Service had a broad margin of error, with the proportion of resistant bacilli in a bacterial population varying greatly. In 1957, the same author[40] analysed strains of *M. tuberculosis* according to eight different resistance criteria in current use at the time. He found that the percentage of strains resistant to INH could vary from 24% to 99% depending on the criteria used. In 1960, Rist and Crofton[41] undertook a survey of drug resistance in 77 hospitals and sanatoria in 18 countries. The techniques used were

analysed according to factors such as growth media, drug concentration ranges, inocula, criteria for resistance, etc. The most striking findings concerned the inoculum size, which varied from 10^2 to 10^8 culturable units, and the minimum concentrations of INH tested, which varied from 0.08 to 1.0 µg/ml.

From this survey, Canetti in 1960 drew the conclusion that international standardization was urgently needed and proposed the creation of an ad hoc committee[42]. Acting on these recommendations, the World Health Organization (WHO) organised a meeting of mycobacteriologists, the outcome of which was reported in 1963. The report outlined the definitions of drug resistance and susceptibility that had been agreed. Susceptibility tests in use at the time were grouped into three categories: the absolute concentration method, the resistance ratio method and the proportion method, and their relative merits were discussed (see section 2.3). Another publication followed in 1969, in which Canetti *et al.* provided detailed descriptions of the three recommended methods[43]. Since then, these international publications have provided the technical standard for the conventional DST of *M. tuberculosis.*

The first concerted international initiative for assessing the proficiency of DST of *M. tuberculosis* came about during a meeting of the Committee on Bacteriology and Immunology of the IUAT in Tokyo in 1973, where a proposal was made for an international collaborative study of the simplification of DST procedures. This proposal was further discussed at a Lagos meeting in 1974 and at a Mexico meeting in 1976. The resulting study was finally reported in 1985[44]. Twenty-three laboratories representing five continents participated.

Two studies were conducted[44]. In the first, most participants used their standard tests which often entailed the use of several drug concentrations and a variety of inocula. The absolute concentration method, the proportion method and two novel methods were used. The results of the first study showed that there were no significant differences between the readings obtained with the absolute concentration method and with the proportion method. Susceptibility to INH, para-amino salicylic acid (PAS) and RMP could generally be accurately determined, but this was not always the case for streptomycin (SM), ethambutol (EMB), ethionamide and thiacetazone. In the second study a simplified absolute concentration method with critical proportion was used by all participants. The analysis of this second study showed that the simplified method was as effective as the recognised older techniques. The drugs for which susceptibility was easiest to determine were INH, PAS, RMP and EMB.

Since this first IUAT-led initiative, there had been no international proficiency testing programme for DST of *M. tuberculosis*. Fittingly, in June 1994, as a prelude to a global anti-tuberculosis drug resistance surveillance project, WHO and IUATLD, which were historically instrumental in bringing about the standardisation and proficiency testing of drug susceptibility procedures for *M. tuberculosis*, convened a meeting in Mainz in which a Supranational Reference Laboratory (SRL) Network was established. The mandate of this international network is to maintain a high level of proficiency in the diagnosis of drug-resistant tuberculosis and to provide quality assurance to National Reference Laboratories (NRL) involved in the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance.

1.4 THE NEED FOR A GLOBAL PROJECT ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

The true magnitude of the problem of anti-tuberculosis drug resistance worldwide is not known. The available information suggests that levels of resistance to anti-tuberculosis drugs may be increasing in some settings[8,36,45]. However, several limitations prevented an adequate assessment of the extent of the problem throughout the world and precluded meaningful comparisons between different countries. These limitations included the absence of *M. tuberculosis* culture facilities and inability to perform anti-mycobacterial susceptibility testing in many countries; the use of laboratory methodologies which were nonstandardised and, in some settings, completely inadequate; selection bias in many surveys, especially those that were hospital based; failure to distinguish primary and acquired drug resistance; and absence of longitudinal studies to detect trends.

Despite the methodological limitations of previously reported surveys, the available data have recently been summarised[45]. A great deal of variability between different countries, regions, and within countries, on reported levels of drug resistance was noted. The prevalence of primary drug resistance for INH as a single agent ranged from 0 to 16.9%, for SM from 0.1% to 23.5%, for RMP from 0 to 3.0%, and for EMB from 0 to 4.2%. As expected, the prevalence of acquired drug resistance was higher than for primary resistance: for INH it varied between 4.0% and 53.7%, for SM between 0 and 19.4%, for RMP between 0 and 14.5%, and for EMB between 0 and 13.7%. The variability observed could be due to methodological error a well as to true differences between countries. High levels of acquired MDR-TB, i.e. resistance to at least INH and RMP, were reported in Nepal (48.0%), Gujarat, India (33.8%), New York City, USA (30.1%), Bolivia (15.3%) and Korea (14.5%). In Europe, strains resistant to INH and RMP were isolated in France, England and Wales, and Germany[45].

In early 1994, the Global Tuberculosis Programme (GTB) at WHO joined forces with the International Union Against Tuberculosis and Lung Disease (IUATLD) and started the Global Project on Anti-tuberculosis Drug Resistance Surveillance. The aims of the Global Project are to measure the prevalence of anti-tuberculosis drug resistance in several countries worldwide using standardised methodology, and to study the correlation between the level of drug resistance and treatment policies in those countries. The overall goal of the project is to improve the performance of NTPs through policy recommendations. The specific objectives are to collect data on the extent of anti-tuberculosis drug resistance by country, particularly in regions identified by WHO as priorities for assistance; to help countries develop a system of surveillance of drug resistance, and improve the diagnostic capacity of laboratories; and, under special circumstances, to revise policy on anti-tuberculosis treatment based on the analysis of the results. This is the first report of the Global Project.

CHAPTER TWO

METHODS

2.1 THE WHO/IUATLD GLOBAL PROJECT ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

The definition of drug resistance in patients with tuberculosis is complicated and requires appropriate microbiological testing. Having recognised the importance of measuring the prevalence of resistance to anti-tuberculosis drugs, WHO and the IUATLD developed a set of standardised methods of surveillance in 1994, and established a Working Group involving international agencies, coordinators of NTPs and investigators in academic institutions throughout the world. The Working Group delineated and later implemented a system to ascertain the global magnitude of the problem of anti-tuberculosis drug resistance. To achieve this objective, two major strategies were agreed upon: 1) standardised surveys and/or surveillance would be implemented on representative samples of tuberculosis patients in various countries; and 2) proper bacteriological methodology in local laboratories would be ensured through proficiency and technical support by the network of SRLs.

As a first step to obtaining internationally comparable results the extent of anti-tuberculosis drug resistance, WHO and IUATLD, in a joint effort with a number of authorities in the field, developed a set of guidelines and distributed them to national governments and interested research institutions[46]. Besides setting the objectives and outlining the strategy needed to achieve them, the guidelines introduced standard definitions and the procedures to implement drug resistance surveillance. The following three basic principles were emphasised in the guidelines: i) a representative sample of tuberculosis patients should be obtained, and the sample size carefully calculated; ii) standard methods of data collection that differentiated between new and retreatment cases of tuberculosis were to be used in order to distinguish between primary and acquired drug resistance; iii) an internationally accepted laboratory methodology was to be used for testing anti-tuberculosis drug resistance, with proficiency testing by an

external, international reference system. These guidelines, first published in 1994, served as the basis for designing the protocols of studies of the prevalence of anti-tuberculosis drug resistance in this report. The guidelines were revised after a meeting of the Working Group in Paris, October 1996, and the 1997 edition is available[46].

2.2 SUPRANATIONAL REFERENCE LABORATORY (SRL) NETWORK

The second step towards obtaining comparable results on the prevalence of anti-tuberculosis drug resistance was to ascertain the accuracy of the susceptibility test procedures used in different laboratories across the world. Selected laboratories were invited to join the network of SRLs based on their international reputation and geographic location. At present (September 1997), the network has 22 laboratories located in North America (Canada, USA), Latin America (Argentina), Europe (Belgium, Czech Republic, France, Germany, Italy, The Netherlands, Portugal, Spain, Sweden, United Kingdom), Africa (Algeria, South Africa), Asia (India, Japan, Korea), and Oceania (Australia) (Map 1).

Inter-laboratory quality control of DST is regularly conducted within the global network. The first such evaluation was implemented in November 1994. Reference strains of *M. tuberculosis* were sent by the coordinating laboratory in Canada to all the other SRLs, which were asked to test the susceptibility pattern of the reference strains with their usual methodology. The susceptibility results of mycobacterial strains were compared to a gold standard that was derived from the results obtained by the majority of the laboratories (judicial criterion). Sensitivity, specificity, and reproducibility of susceptibility testing were calculated for each supranational laboratory and for each of the four drugs tested, i.e., SM, INH, RMP, and EMB[47]. Global strain exchange exercises were repeated within the network in 1995 and 1996. A fourth round has just been completed in 1997.

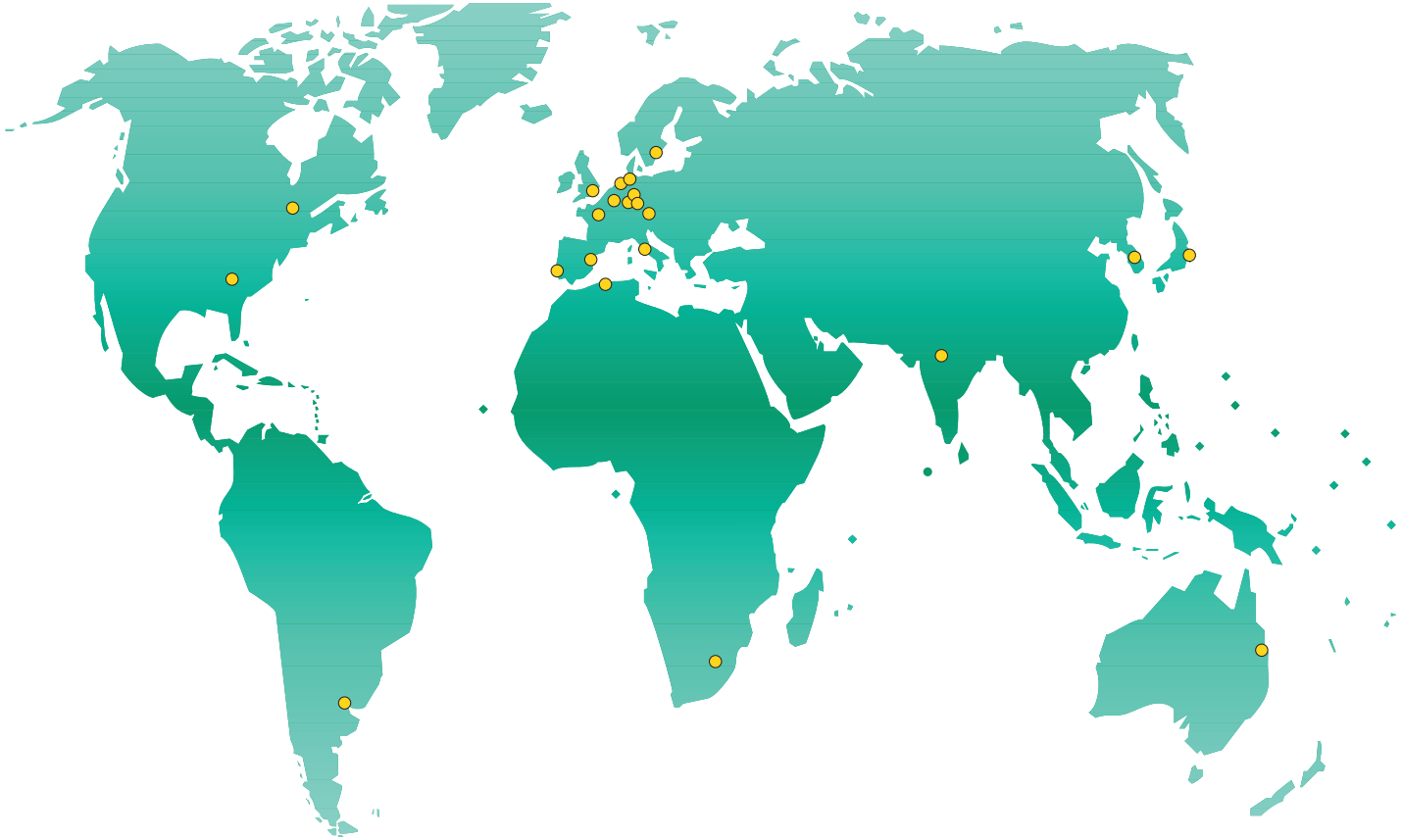
2.3 METHODS OF LABORATORY DIAGNOSIS OF ANTI-TUBERCULOSIS DRUG RESISTANCE

The three conventional DST methods described in this section have been standardised and are widely used throughout the world to measure drug resistance of *M. tuberculosis*[43,48,49]. In general, participating laboratories used the DST method with which they were most familiar in order to eliminate variability due to disruption of routine testing induced by changing over to a new procedure. Molecular biology techniques were not standardised and, although used in a few laboratories for DST, they are not analyzed in this monograph.

2.3.1 The absolute concentration method

This test was used originally to determine the minimal inhibitory concentrations (MICs) of INH and SM by adding a carefully controlled inoculum of *M. tuberculosis* to the control and drug-containing media[43]. Media containing several sequential two-fold dilutions of each drug are used, and resistance is indicated by the lowest concentration of the drug which will inhibit growth (i.e., less than 20 colonies at the end of 4 weeks).

Map 1. The WHO/IUATLD Network of Supranational Reference Laboratories (SRLs), 1997



● Location of each SRL providing quality assurance in anti-tuberculosis drug susceptibility testing

MAP 1

A satisfactory test can only be obtained if the inoculum size and the drug concentrations are standardised in each laboratory by reference to a "wildtype" culture. Because of the strict inoculum standardization required, this technique may be less reliable than the three following.

Methods of laboratory diagnosis of anti-tuberculosis drug resistance

- The absolute concentration method.
- The resistance ratio method.
- The proportion method and its variants.
- The BACTEC 460® radiometric method.

2.3.2 The resistance ratio method

This test, a variant of the absolute concentration method, was first introduced to prevent variation in MICs of a given strain of *M. tuberculosis* when tested on different batches of drug-containing media[43,48]. The resistance ratio is defined as the MIC of the test strain divided by the MIC of the standard susceptible strain H37Rv in the same set of tests. A resistance ratio of 2 or less defines drug susceptibility, while 8 or more is considered evidence of drug resistance; strains with intermediate drug resistance are rare.

Satisfactory performance of this test still depends on the standardization of the inoculum size, but the critical concentration need not be determined because a susceptible control is provided by the standard strain.

2.3.3 The proportion method

Originally described at the Pasteur Institute in Paris[39], this technique has gained acceptance in many countries throughout the world. With this approach, the ratio between the number of colonies growing on drug-containing medium and the number of colonies growing on drug-free medium indicates the proportion of drug-resistant bacilli present in the bacterial population. A high and a low dilution of the inoculum are planted on the media so that isolated, countable colonies can be obtained with at least one of the dilutions. From these bacterial colony counts, the proportion of mutants resistant to the drug concentration tested can be determined and expressed as a percentage of the total number of viable colony forming units in the population. Below a certain fraction, called the "critical proportion", a strain is classified as susceptible; above that, as resistant. The significant resistance proportion levels for the different anti-tuberculosis drugs are the levels above which the drugs are estimated not to be clinically useful.

Standardization of the inoculum size in the proportion method is not crucial as long as isolated colonies can be detected at one of the two dilutions plated. Another advantage of this technique is that it is the only one in which the validity of critical drug concentrations and drug resistance proportions have been correlated to bacteriological as well as clinical criteria[47,50]. As in the case of the resistance ratio method, this technique is based on conventional culture and it may take over 2 months from receipt of primary specimens before DST results are obtained.

2.3.4 The BACTEC 460® radiometric method

A computerised system (BACTEC®) was commercially developed for DST in liquid medium[51]. This rapid method was developed in the 1980s and is now in routine use in many industrialised countries[49]. It is a variant of the proportion method in which production of ^{14}C-labeled CO_2 (evidence of bacterial growth) in a standard *M. tuberculosis* inoculum in the presence of antimicrobials is compared to the labeled CO_2 produced by a 1/100 dilution of the original inoculum in the absence of antimicrobials. Results can be obtained within one week following inoculation, but the technique requires the appropriate laboratory infrastructure (including nuclear waste disposal), and it is more expensive than the nonradiometric proportion method.

2.4 STANDARDIZATION AND QUALITY ASSURANCE OF DRUG SUSCEPTIBILITY TESTING

Three strain exchange exercises were conducted to ensure inter-laboratory consistency in DST throughout the network, starting in November 1994. As mentioned above, reference strains of *M. tuberculosis* were sent by the coordinating laboratory in Canada to all the other SRLs. The DST results of all the SRLs were then compared. The following paragraphs summarise the standardised materials and procedures followed by the SRLs.

2.4.1 Anti-tuberculosis drugs tested

This project focuses on resistance to four of the first-line anti-tuberculosis drugs, INH, RMP, EMB and SM, which were tested by all countries in the Working Group. These drugs were chosen because they are and have been widely used throughout the world; drug resistance can be reliably measured by standardised techniques; they have been studied for many years; and background knowledge already exists on levels of resistance to which new information can be added. Given the poor reliability of DST results obtained when using low pH solid growth media[43], PZA was not included in the drug panel of this Global Project. Further, thiacetazone is not used as widely as the other drugs and drug susceptibility assays for it are less reliable[43]. The susceptibility of *M. tuberculosis* to second-line agents such as ofloxacin, PAS, ethionamide, cycloserine and newer drugs was evaluated only in a few laboratories and is not included in this report.

INH, RMP, ethambutol dihydrochloride, dihydrostreptomycin sulphate and streptomycin sulphate were used for laboratory testing. The dihydro derivative of streptomycin sulphate was used in egg-containing growth media because it is more stable than SM. Antimicrobial base powders were supplied to all sites by the coordinating laboratory to eliminate the source of the drugs as a possible cause for discrepancy in the results. This arrangement was maintained during the various rounds of proficiency testing[47].

2.4.2 Mycobacterial cultures

Identical sets of 10 clinical isolates of *M. tuberculosis* in duplicate (20 cultures) were sent to the laboratories in the network in each round of proficiency testing. Participants knew beforehand that the panel comprised 10 pairs of cultures. The sample

size, i.e. 20 cultures, was calculated to yield a significance level of ∝=0.05 to be able to detect a true difference between laboratory methods with a power of 90%[47].

To maintain confidentiality of each SRL's results, each site received an identifying number known only to the individual laboratory and to the coordinator. The cultures were identified by randomly chosen numbers which varied from site to site. The culture panel included both drug susceptible - including reference strain H37Rv - and drug-resistant isolates encompassing some commonly encountered resistance marker combinations. The prevalence of resistance in the reference strains tested in the first round, for example, was 50% for INH, 10% for RMP, 20% for EMB, and 70% for SM. The transportation of specimens between SRLs was conducted following international guidelines[52,53,54].

2.4.3 Drug susceptibility testing (DST)

In the planning stage of this project, as mentioned in the preceding section, it was decided to allow the participating laboratories to use the method each was most familiar with in order to eliminate variability due to disruption of routine testing. The conventional DST methods evaluated were the absolute concentration method, the resistance ratio method and the proportion method[43,48]. The radiometric BACTEC 460® procedure based on the proportion method was also included[49]. These techniques are described in section 2.3. Laboratories were to adhere strictly to the detailed procedures described in the references cited above. Laboratories reported results to the WHO Collaborating Center for Tuberculosis Bacteriology Research, Ottawa, Canada, for collation and analysis.

2.4.4 Participants in the proficiency testing

In the first round of proficiency testing, 16 laboratories participated. Seven were located in Europe, two in the Americas, two in Asia and two in Africa. Nine laboratories reported results obtained with the proportion method on Loewenstein-Jensen (L-J) medium, and three reported those obtained with the German Standard Deutsche Industrie Norm (DIN) modification of the proportion method on L-J medium[55]. One laboratory reported results using a modified proportion method on L-J medium where the critical concentration for resistance to SM is 10.0 mg/ml, and another laboratory reported results obtained with the proportion method on Middlebrook 7H-10 medium. One laboratory reported results obtained with the BACTEC 460® radiometric method and another used the resistance ratio method.

In the second round, a laboratory from Oceania using the BACTEC® method — one from Asia using the proportion method on L-J, and one from Europe using a modified absolute concentration method on Middlebrook 7H10 agar, joined the network. In the third round of testing, one laboratory from Europe using the resistance ratio method and one from the Americas using the proportion method on 7H11 agar joined the network. Two additional European reference laboratories joined the network in 1997, to give a total of 22 SRLs.

2.4.5 Analysis of the results of proficiency testing

Results were blinded and interpreted by the participating laboratories as originally recommended[43]. Cultures were classified as *resistant* or *susceptible*. Actual colony counts

or Growth Index readings were to be kept by each laboratory for evaluation purposes. Results were compared to the judicial results, i.e. the agreement of the majority of the participating laboratories was considered the "gold standard"[47]. Where significant differences were found in the results of a given laboratory compared to those of the group as a whole, the director of the laboratory was contacted to attempt to determine possible causes for the discrepancy.

A programme designed with Lotus 123 v.4 software was used to interpret the data. This analysis yields values for sensitivity, i.e., ability to detect true resistance; specificity, i.e., ability to detect true susceptibility; efficiency (or overall accuracy), i.e., fraction of the number of correct results and the total number of results; and intralaboratory reproducibility (or reliability) between duplicate cultures expressed as percent agreement[56]. The analysis of variance (ANOVA) test was used to test the differences between laboratories and between drug susceptibility results. The data from proficiency testing are presented in section 3.3.

2.5 COORDINATION OF NATIONAL SURVEYS

From 1994 to 1996, WHO and IUATLD promoted surveys of the prevalence of anti-tuberculosis drug resistance in several countries in collaboration with NTPs and local research institutions. The essential eligibility criterion for country participation was the existence of at least one functioning central culture laboratory linked to the majority of the tuberculosis diagnosis centres. The network of countries performing drug resistance surveys or surveillance according to the WHO/IUATLD guidelines is still expanding (Table 2). This report includes the results for the first 35 surveys completed to date (Map 2). Ten more countries have ongoing surveys and more are scheduled to begin such projects in the coming months (Map 2).

2.5.1 Coordinating team

Each survey of the prevalence of anti-tuberculosis drug resistance involved three major operational levels. The NTP provided leadership and support, as well as training and other resources. The NRL processed each of the specimens from eligible patients, and underwent proficiency testing by a SRL. Individual diagnostic centres were involved in the selection of patients and collection of the appropriate clinical information. In general, the coordinating team of each survey contained members from each of these three levels, as well as an epidemiologist.

The head of the NTP or the Director of the NRL, or their designee, took charge of the national survey coordinating team. With official backing and appropriate scientific consultation, the coordinating team was responsible for planning and carrying out the survey, the quality assurance of DST, and for standardised reporting of the results to the Global Project coordinator at WHO. Countries with ongoing drug resistance surveillance programmes maintained their structure and function.

Table 2. WHO/IUATLD Network of Supranational Reference Laboratories and functioning National Reference Laboratories (September 1997)

Supranational Reference Laboratory	Country or territory	Status	National Reference Laboratory
Institut Pasteur Algiers, Algeria	Benin	Ongoing survey	Laboratoire de Référence pour la Tuberculose, Institut National de Pneumophtisiologie, Cotonou.
	Guinée	Planning stage	(To be determined)
	Ivanovo Oblast, Russia	Ongoing survey	Central Tuberculosis Research Institute, Moscow
	Tunisia	Planning stage	(To be determined)
INPPAZ - Instituto Panamericano de Proteccion de Alimentos y Zoonosis Buenos Aires, Argentina	Argentina	Survey completed	National Institute for Microbiology C. Malbrán.
	Bolivia	Survey completed	Instituto Nacional de Salud, INLASA, La Paz.
	Brazil	Survey completed	Centro Referéncia "Prof. Hélio Fraga", Rio de Janeiro.
	Chile	Ongoing survey	Instituto de Salud Pública de Chile, Santiago de Chile.
	Paraguay	Ongoing survey	Laboratorio Central de Tuberculosis, Asunción.
	Peru	Survey completed	Instituto Nacional de Salud, Lima, Hospital "Daniel A. Carrión", Callao, and Hospital Nacional "Cayetano Heredia", Lima.
Queensland Health - Mycobacterial Reference Laboratory. Brisbane, Australia	Australia	Ongoing surveillance	The SRL itself.
	India, TamilNadu State	Ongoing survey	Tuberculosis Research Center, Madras.
	New Zealand	Ongoing surveillance	TB Reference Laboratory, Green Lane Hospital, Auckland.
Institute of Tropical Medicine Antwerpen, Belgium	Congo-Brazzaville	Planning stage	(To be determined).
	Romania	Survey completed	"M. Nasta" TB Institute, Bucharest.
Laboratory Centre for Disease Control. Ottawa, Canada	Cuba	Ongoing surveillance	Instituto de Medicina Tropical "Pedro Kourí", Havana.
	Dominican Republic	Survey completed	Central Veterinary Laboratory, Santo Domingo.
	France	Ongoing surveillance	National Reference Centre for the Surveillance of TB, Paris
	Nicaragua	Ongoing survey	Ministerio de Salud, Managua.
National Institute of Public Health. Prague, Czech Republic	Slovak Republic	Planning stage	To be determined.
Institut Pasteur, Centre National de Référence des Mycobactéries. Paris, France	Côte d'Ivoire	Survey completed	Laboratoire de Référence du Programme National de Lutte contre la Tuberculose (PNLT), Abidjan, and Centre de Diagnostic et de Recherche sur le SIDA et les maladies opportunistes (CEDRES), Abidjan.
	Italy	Survey completed (only HIV+)	Laboratorio di Micobatteriologia, University of Bari, Italy.
Forschungsinstitut Borstel. Borstel, Germany	Uganda	Ongoing survey	Central Tuberculosis Laboratory, Kampala
	Zimbabwe	Survey completed	National TB Reference Laboratory, Bulawayo.
Kuratorium Tuberkulose in der Welt E.V. Gauting, Germany	Nepal	Survey completed	GENETUP National Tuberculosis Centre and Laboratory, Kathmandu.
Medizinisch-diagnostisches Institut-Fatol Arzneimittel. Schiffweiler, Germany	Hungary	Planning stage	"Korányi" National Institute of TB and Pulmonology, Budapest.
Armauer Hansen Institut - DAHW. Würzburg, Germany	Sierra Leone	Survey completed	No NRL. All drug susceptibility testing performed by the SRL.
	Uganda	Planning stage	Central Tuberculosis Laboratory, Kampala..

…continued

New Delhi Tuberculosis Centre. New Delhi, India	Delhi State, India 4 Northern States, India	Survey completed Ongoing survey	The SRL itself. The SRL itself.
Istituto Superiore di Sanità. Rome, Italy	Italy	Planning stage	Istituto Villa Marelli, Milan.
The Research Institute of Tuberculosis. Tokyo, Japan	Iran Malaysia Singapore	Planning stage Ongoing survey Ongoing survey	National Research Institute of Tuberculosis and Lung Disease, Tehran Institute of Respiratory Medicine, Kuala Lumpur. Department of Respiratory Medicine, Ten Tock Seng Hospital, Singapore.
Korean Institute of Tuberculosis. Seoul, Korea	Henan Province, China Hong Kong, China Korea Shandong Province, China Thailand Vietnam	Survey completed Survey completed Survey completed Ongoing survey Ongoing survey Ongoing survey	Henan Anti-tuberculosis Institute, Henan. Yung Fung Shee Memorial Centre, Hong Kong. The SRL itself. Beijing Tuberculosis & Lung Tumor Research Institute, Beijing. Laboratory of Tuberculosis Division (DCDC), Ministry of Health, Bangkok. National Institute of TB & Respiratory Diseases, Hanoi. National Reference Laboratory, Ho Chi Minh City.
National Institute of Public Health and Environmental Protection (RIVM). Bilthoven, The Netherlands	Netherlands Poland	Ongoing surveillance Ongoing survey	(Various laboratories under coordination by SRL itself) National TB & Lung Disease Research Institute, Warsaw.
Instituto Nacional de Saude. Porto Portugal	Portugal	Ongoing survey	The SRL itself.
National Tuberculosis Research Programme-MRC. Pretoria, South Africa	Lesotho South Africa Swaziland Tanzania	Survey completed Ongoing survey Survey completed Planning stage	No NRL. All drug susceptibility testing performed at the SRL. The SRL itself. No NRL. All drug susceptibility testing performed at the SRL. National Institute for Medical Research, Dar-es-Salaam.
Institut Català de la Salut, CSU "Vall d'Hebron". Barcelona, Spain	Barcelona, Spain Czech Republic	Survey completed Survey completed	The SRL itself. National Institute of Public Health, Prague.
Swedish Institute for Infectious Disease Control, Karolinska. Stockholm, Sweden	Estonia	Survey completed	Tuberculosis Reference Laboratory, Tartu.
PHLS Mycobacterium Reference Unit. London, UK	Gambia Kenya UK, England and Wales UK, Northern Ireland UK, Scotland	Planning stage Survey completed Ongoing surveillance Ongoing surveillance Ongoing surveillance	MRC Laboratory, Banjul Kemri Respiratory Disease Research Unit, Nairobi. The SRL itself. Northern Ireland Reference Laboratory/MRV. Scottish Mycobacteria Reference Laboratory, Edinburgh.
Centers for Disease Control and Prevention-CDC. Atlanta, USA	Botswana Latvia México Puerto Rico USA	Survey completed Ongoing survey Ongoing survey Ongoing surveillance Ongoing surveillance	National Health Laboratory, Gaborone. State Centre of Tuberculosis and Lung Diseases, Riga. Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (INDRE), México City. Laboratorio Central de Tuberculosis, San Juan. (Multiple state and local laboratories following national standards.)

2.5.2 Survey protocols

The coordinating team in each country, often in consultation with their SRL, developed a protocol specifying the procedures for sampling, interviewing patients, and susceptibility testing, that was modeled on the WHO/IUATLD international guidelines. These protocols were reviewed by and discussed with WHO before the implementation phase, with special emphasis on sample size calculation, sampling strategies, determination of previous treatment, laboratory methods, timetable, and budget. Funding was arranged from national, bilateral, non-governmental, and WHO sources to ensure completion of each survey.

2.5.3 Diagnostic centres

Diagnostic centres in the region or country where TB suspects were screened, decisions on diagnosis were made, and tuberculosis patients treated, were included in the study. Most diagnostic units were small, non-specialised health centres and clinics, usually run by the government, or outpatient departments of hospitals. Private sector institutions and general practitioners were generally not included as diagnostic centres, unless their activities were based on some agreement with the NTP and they were following national guidelines for diagnosis and treatment. All the materials necessary for the survey, such as patient forms and laboratory supplies, were available in each centre at the start of the survey.

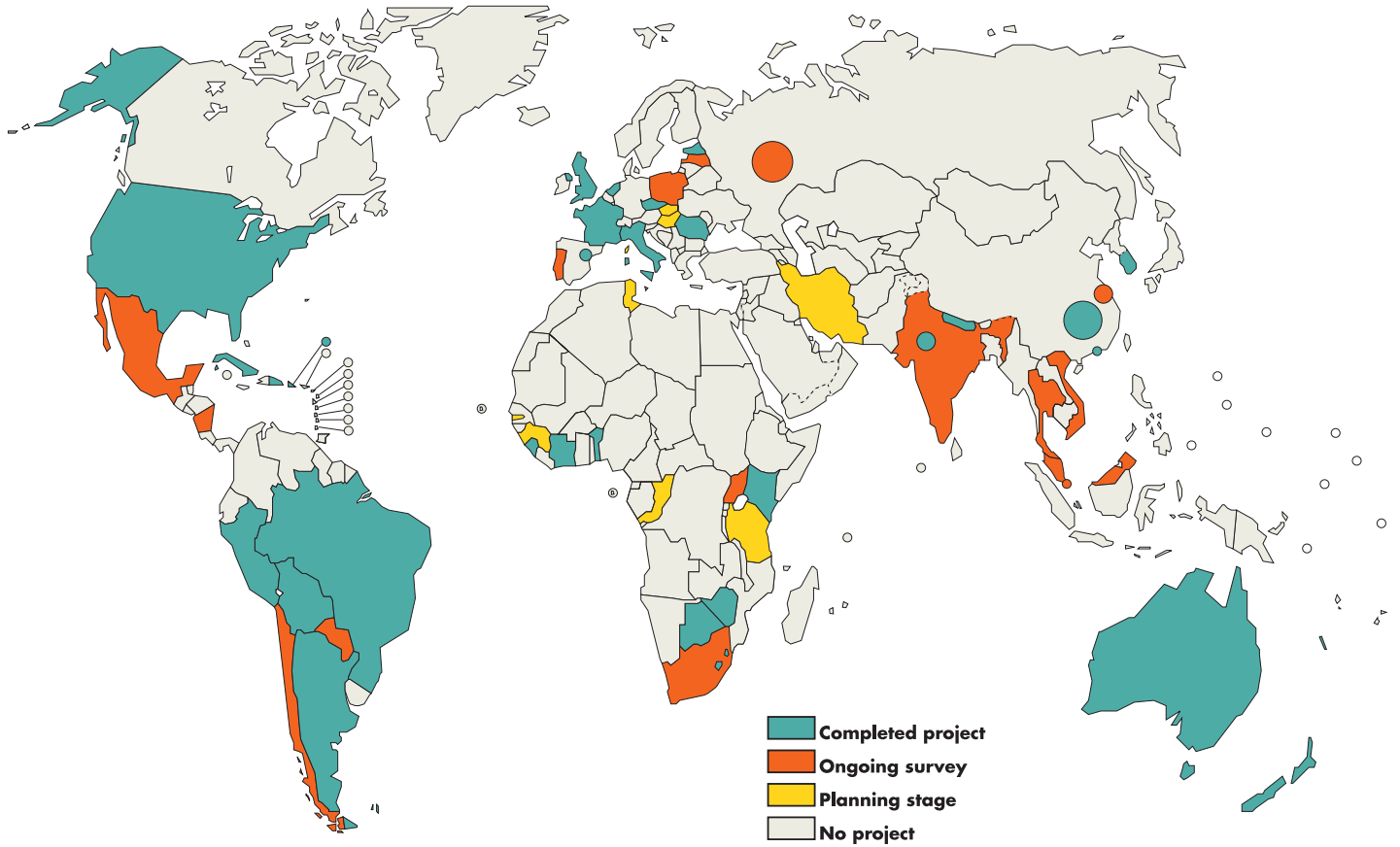
2.5.4 Training

Before actual surveys started, the coordinating team that addressed all technical, administrative and logistic procedures developed a simple manual or protocol which was distributed to health officers participating in the survey. Training focused on patient enrolment, obtaining reliable data on prior anti-tuberculosis treatment, and laboratory techniques; pilot phases were encouraged, but not universally done. In most places, the health providers in charge of the patient evaluation were identified in each diagnostic centre involved in the survey and were briefed on the purpose of the survey and provided with the necessary training and forms. Training of peripheral laboratory staff generally focused on preparation and reading of smears, decontamination of sputum samples, storage and transport of samples, and proper registration. Countries with ongoing surveillance simply continued their established procedures.

2.5.5 The National Reference Laboratory (NRL)

The NRL, which was the reference institution in the country, prepared cultures from the sputum samples and performed strain identification and susceptibility testing. When there were peripheral culture laboratories, strains instead of sputum samples were submitted to the NRL. In many instances, coordinators from the SRL visited the NRL prior to the beginning of the survey. Testing was performed either following the guidelines provided or, after agreement with a SRL, following the procedures established nationally. The results of susceptibility tests done by the NRL were validated by external quality assurance programmes, organised by the SRL, as described in section 2.9.3. International guidelines on shipment of infectious material were followed[52,53,54].

Map 2. The WHO/IUATLD Working Group on Global Drug Resistance Surveillance in Tuberculosis, 1997.



MAP 2

2.6 DEFINITIONS AND TERMINOLOGY

2.6.1 Drug resistance

Drug resistance is defined as a decrease in the in-vitro susceptibility of *M. tuberculosis* of sufficient degree to be reasonably certain that the strain concerned is different from a wild strain that has never come into contact with the drug. Following WHO/IUATLD Guidelines, resistance to each of the four anti-tuberculosis drugs was determined according to the results of bacteriological testing (see Section 2.3). The term monoresistance is used when a strain is resistant to only one of the four drugs tested; polyresistance is used to signify resistance to more than one of these drugs. *Multidrug resistance* is defined as resistance to both INH and RMP, with or without resistance to additional agents. These two drugs represent the most potent combination against the tubercle bacillus[57], and constitute the mainstay of anti-tuberculosis treatment[28,58].

2.6.2 Acquired drug resistance

Patients diagnosed with tuberculosis and started on anti-tuberculosis treatment, whose bacilli then develop drug resistance to one or more of the medications used during treatment, are said to have developed "acquired (or secondary) drug resistance". This can only be demonstrated if the baseline susceptibility to a given drug was documented before treatment with the specified drug was given. In most settings, however, documentation of drug susceptibility before the initial treatment is not available.

The surveys reported here defined acquired drug resistance as resistance found in a patient who had previously received at least one month of anti-tuberculosis treatment, as documented in the tuberculosis registry, or medical records or by the patient's account. Acquired resistance may thus be found in culture positive cases in the following categories: patients with treatment failure; patients who relapse after successful completion of treatment; and patients who return after treatment interruption, including chronic, recalcitrant cases. These definitions and terms are consistent with those described in the WHO Framework for Effective Tuberculosis Control[59].

2.6.3 Primary drug resistance

Primary drug resistance is found in patients who have never received any anti-tuberculosis medication in the past, i.e., patients infected with a drug-resistant strain. As the history of anti-tuberculosis treatment is frequently inaccurate, primary drug resistance is difficult to ascertain in practice. The pragmatic approach to estimate the approximate prevalence of primary drug resistance is to include every patient presenting with an organism resistant to one or more anti-tuberculosis drugs prior to commencement of therapy and without any evidence of previous treatment. The alternative term "initial drug resistance" has been proposed for such situations. However, the systematic use of this alternative concept encourages the omission of a thorough investigation into the history or documentation of prior treatment[60].

In the Global Project, primary drug resistance was defined as the presence of resistant strains of *M. tuberculosis* in a patient who, in response to direct questioning, denies having had anti-tuberculosis treatment for more than a month and, in countries

where adequate documentation is available, no evidence of such history exists. In Nepal and Vietman, patients with any previous treatment were excluded. As part of the WHO/IUATLD Guidelines, a standardised algorithm was provided to ascertain history of prior treatment. Chronic pulmonary scarring in chest radiographs was to prompt a reinterrogation, although radiography was not routinely available in many of the countries. When available, medical records and state registers were checked. Charts or specimens of common anti-tuberculosis drug presentations to assist patient recollection were not systematically used in these surveys. When the duration of prior treatment could not be determined at less than one month, patients were classified as previously treated.

Definitions of drug resistance

- *Acquired drug resistance* is that which is found in a patient who has received at least 1 month of prior anti-tuberculosis drug treatment.
- *Primary drug resistance* is the presence of resistant strains of *M. tuberculosis* in a patient with no history of such prior treatment.
- *Combined drug resistance* is the prevalence of drug resistance among all cases of tuberculosis, regardless of prior drug treatment, in a given year and country.
- *Multidrug resistance (MDR)* is defined as resistance to at least INH and RMP, the two most potent drugs and the mainstay of anti-tuberculosis treatment.

2.6.4 Combined prevalence of drug resistance

Despite the importance of distinguishing between primary and acquired drug resistance, the combined prevalence of drug resistance is also useful for a variety of reasons. At the practical level, two countries with ongoing surveillance (Australia and the Netherlands) and the survey in New Delhi could not reliably ascertain history of prior treatment, even though their overall estimates of drug resistance were based on representative samples of tuberculosis patients. More importantly, the combined prevalence of anti-tuberculosis drug resistance represents an approximation to the proportion of drug-resistant strains circulating in the community. Accordingly, today's combined levels of drug resistance will be an important determinant of tomorrow's prevalence of primary drug resistance.

To obtain combined estimates of drug resistance for countries reporting primary and acquired prevalence separately we used two different approaches. In the countries conducting drug resistance surveillance of 100% of their tuberculosis patients, we simply combined the individual data in patients with and without previous anti-tuberculosis treatment. In countries conducting surveys, regardless of the different sampling schemes for patients with and without prior treatment, we also combined their separate reports. However, instead of using the proportions of the two subgroups as reported, the contribution of acquired drug resistance was weighted by the proportion of retreatment cases (i.e., treatment failures, return after default, relapses) among all cases registered for treatment in the whole country, according to 1995 reports to the WHO by the NTPs. In most instances, this figure closely matched the reported proportion of previously

treated patients in those surveys with systematic sampling of all patients registered for treatment.

2.6.5 Additional terms used in this document

A *wild strain* is defined as a strain of *M. tuberculosis* complex which has never been exposed to any antimycobacterial drug. *Naturally resistant strains* are wild strains with species-specific, constitutional resistance to a specific drug, such as *M. bovis* resistance to PZA[61] or *M. tuberculosis* resistance to penicillin. *Wild-type resistance* is the result of random mutation in naturally susceptible strains before any exposure to anti-tuberculosis drugs[62].

Anti-tuberculosis chemotherapy refers to treatment based on the most frequently used drugs, namely INH, RMP, PZA, SM, EMB and thiacetazone. *Short course chemotherapy (SCC)*, the treatment regimen recommended by WHO, consists of 2 months of INH, RMP and PZA, plus a fourth drug (SM or EMB), followed by 4 months of INH and RMP (or, alternatively, 6 months of INH and EMB or thiacetazone)[28]. *Directly observed therapy* means literally watching a patient ingest (or be given parenterally) the prescribed anti-tuberculosis treatment. *Fix-dose combination (FDC) drugs* are commercially available products such as the combinations of INH + RMP + PZA, INH + RMP, INH + thiacetazone, and the less commonly used combination of INH, RMP and EMB. Combinations of INH and vitamins are not considered FDC drugs.

Treatment outcomes are categorised by WHO into mutually exclusive categories for the purpose of cohort analysis[59,63]. *Cure* is an initially smear positive patient who completed therapy and had negative sputum smear results at completion of treatment. *Treatment completion* refers to a smear positive patient who completes treatment with a negative sputum smear result at the end of the initial phase, but with no sputum smear result at the end of treatment (*Treatment success* includes both cure and treatment completion). *Death* is recorded for patients who die during treatment regardless of the cause. *Treatment failure* occurs when a smear positive patient remains or becomes smear positive again five months or more after commencing treatment. *Treatment interruption* ("default") cases are patients who, at any time after registration, do not collect their treatment drugs for two months or more. Patients who move to another reporting unit and whose treatment results are unknown are classified as having been *transferred out*. Finally, a *relapse* is a patient previously declared cured and diagnosed again with smear positive tuberculosis[59,63].

2.7 SURVEY AREAS AND SAMPLING STRATEGIES

Most countries included in this analysis performed cross-sectional surveys during 1995 and 1996. Several countries conduct ongoing surveillance of drug resistance, including Australia, Cuba, the Netherlands, New Zealand, the United Kingdom and the United States (including Puerto Rico); data from their 1995 (and 1996) reports are included in this monograph. The rest of the countries included conducted *ad hoc* surveys and the methodology is detailed below (Table 3).

Table 3. Sampling methodology in the Global Project

COUNTRY	REPORT YEAR	PROJECT STATUS	TOTAL DURATION	TARGET AREA (MONTHS)	SAMPLING METHOD	FRACTION SAMPLED (%)*
Argentina	1994	Completed survey	6	Countrywide	Cluster	30
Australia	1995	Ongoing surveillance	12	Countrywide	All cases	100
Benin	1995-1997	Completed survey	24**	Countrywide	Proportionate clusters	23
Bolivia	1996	Completed survey	11**	Countrywide	Cluster	40
Botswana	1995-1996	Completed survey	22**	Countrywide	Random	10
Brazil	1995-1996	Ongoing survey	14**	Nearly countrywide	Proportionate clusters	5
China (Henan province)	1996	Ongoing survey	9	Province	Proportionate clusters	7
Cuba	1995-1996	Ongoing surveillance	12	Countrywide	Proportionate clusters	52
Czech Republic	1995	Completed survey	6	Countrywide	All cases	100
Dominican Republic	1994-1995	Completed survey	21**	Countrywide	Proportionate clusters	20
England & Wales	1995	Ongoing surveillance	12	Countrywide	All cases	100
Estonia	1994	Completed survey	12	Nearly countrywide	All cases	100
France	1995-1996	Ongoing surveillance	24	Sentinel sites	All cases	100
India (Delhi state)	1995	Completed survey	6	State	All cases	100
Italy	1994	Completed survey	18**	HIV population	Cluster	32
Ivory Coast	1995-1996	Completed survey	12	Countrywide	Proportionate clusters	5
Kenya	1995	Completed survey	5	Nearly countrywide	Proportionate clusters	15
Latvia	1996	Ongoing survey	6	Countrywide	All cases	100
Lesotho	1994-1995	Completed survey	18	Countrywide	Proportionate clusters	35
Nepal	1996	Completed survey	6	Sentinel sites	All cases	100
Netherlands	1995	Ongoing surveillance	12	Countrywide	All cases	100
New Zealand	1995-1996	Ongoing surveillance	12	Countrywide	All cases	100
Northern Ireland	1995	Ongoing surveillance	12	Countrywide	All cases	100
Peru	1995-1996	Completed survey	4	Countrywide	Proportionate clusters	20
Portugal	1995	Completed survey	24	Countrywide	All cases***	20
Puerto Rico	1994-1996	Ongoing surveillance	36	Island-wide	All cases	100
Republic of Korea	1994	Completed survey	3	Countrywide	All cases	100
Romania	1995	Completed survey	12**	Countrywide	All cases	100
Russia (Ivanovo Oblast)	1995-1996	Ongoing survey	12	Oblast	All cases	100
Scotland	1995	Ongoing surveillance	12	Countrywide	All cases	100
Sierra Leone	1995-1996	Completed survey	24**	Nearly countrywide	Random	15
Spain (Barcelona)	1995-1996	Completed survey	20	Citywide	Cluster	65
Swaziland	1994-1995	Completed survey	18	Countrywide	Proportionate clusters	20
Thailand	1996-1997	Ongoing survey	6**	Countrywide	Proportionate clusters	13
United States of America	1995	Ongoing surveillance	12	Countrywide	All cases	100
Viet Nam	1996-1997	Ongoing survey	10**	Countrywide	Random clusters	100
Zimbabwe	1994-1995	Completed survey	30**	Nearly countrywide	All cases	100

*Sampled fraction of all eligible tuberculosis patients in the target area and period.
**Patient enrolment was rotated every two to three months in different districts of the country.
***All cases targeted but only a fraction sampled due to strict exclusion criteria (e.g. 1 dose of treatment before coordinating team could obtain culture).

It should be noted that England and Wales, Scotland and Northern Ireland have independent surveillance systems and reported the ecological characteristics (including population) of their regions separately. Thus they are analyzed individually in this report. However, the UK is a single entity within the 216 countries and territories monitored by WHO; analyses at that level used the average estimates of the three regions within the UK. In addition, although part of the Working Group, Italy's results were excluded from the analysis because only HIV-infected patients were studied and the survey coincided with a MDR-TB nosocomial outbreak. The results from the Henan Province in China were not analysed because their DST results were being verified at the time of this publication.

2.7.1 Survey target areas

For each survey, the target population was made up of all registered cases of smear positive tuberculosis in the survey area. In most countries, the survey area was the entire country. In Nepal and Sierra Leone, the survey area excluded some centres *a priori* because of logistic problems primarily related to access (i.e., remote regions, war zones, etc) but not because of the quality of the local control programme. Surveys in such large countries as Russia, China and India were restricted to a single large province. In France, the surveyed area was composed of selected sentinel sites (Table 3). The surveys in Thailand and Vietnam are still ongoing, and their results included in this monograph should be considered preliminary.

2.7.2 Sample size of individual surveys

The sample size was calculated from the expected prevalence of RMP resistance, or the drug with the lowest prevalence of resistance, which was estimated from previous studies or based upon data available from the national TB programme; in the absence of previous data the educated guess of investigators was used[64]. The precision of the calculated 95% confidence intervals (1 to 3 percent points) was balanced by the size of the tuberculosis patient population and recruitment logistics in individual countries.

When cluster sampling was used, the calculated sample size was multiplied by two to account for the design effect[64]. Sample size requirements were further increased by 5%-20% to account for expected losses (patients not returning to provide sputum samples for culture, specimens that were contaminated or did not grow in the laboratory, or uninterpretable DST results). When replacement was required, it was done with other patients diagnosed in the centre concerned and according to the sampling method planned. Table 3 provides information on sampling methodology by country.

2.7.3 Sampling strategies

All surveys included either all eligible patients (i.e., census or surveillance) or a randomly or systematically selected sample of patients[65]. Given the small proportion of cases with history of prior treatment, all such cases were included in the surveys (100% sampling) in order to avoid the longer intake period that would be required if only a small fraction was sampled; care was taken not to enroll any patient twice. In order to select representative tuberculosis patients without history of previous treatment, different sampling strategies were adopted by individual countries[65].

2.7.3.a *100% sampling of all diagnostic centres*

All eligible patients in each diagnostic centre were included within a given intake period. This straightforward census of all consecutive cases, when feasible, gives the best representation of the patient population diagnosed with tuberculosis. Large and small diagnostic centres in ambulatory or hospital settings are represented proportionally. In some countries, routine surveillance was already in place to include every patient in the country. Most countries, however, did not have such systems and, while still selecting all patients from all diagnostic centres, the duration of their survey was limited to the required sample size.

The duration of the intake period was calculated by dividing the required sample size by the total number of patients diagnosed with smear positive disease in a year in a given country. In a third of the surveys patient enrolment was rotated in different regions in blocks of 2 or 3 months. This prevented the saturation of central laboratory facilities performing cultures and susceptibility testing, and allowed the coordinating team to focus resources and attention on separate geographic regions at a time. The technique was discouraged when the total time to complete the study exceeded 1 year, given the analytical complications related to trends and changes in national control policies.

2.7.3.b *Simple random sample*

The required number of subjects was drawn at random from the expected number of sputum smear positive patients in a country during a given period. Care was taken not to disrupt the clinical and administrative routines of individual tuberculosis diagnostic centres. Random selection of cases from each diagnostic centre was done only in one country (Botswana) due to logistical problems and cost.

Sampling strategies for Drug Resistance Surveillance

- Countrywide, ongoing surveillance of the population.
- Surveys with 100% sampling during a specified time period.
- Surveys with a simple random sample of TB patients.
- Surveys of randomly selected clusters of patients (i.e., diagnostic centres).
- Surveys with population proportionate cluster sampling.

2.7.3.c *Cluster sampling*

When this approach was used, diagnostic centres in the country were randomly selected and all sputum smear positive patients seen in those centres during a defined intake period were included in the survey. The intake period was identical for all centres, resulting in a balanced sample with centres represented according to their share of cases in the control programme. A minimum number of 30 clusters was recommended to avoid biased estimates of the prevalence of drug resistance given differences in types and size of diagnostic centres. In areas where the number of diagnostic centres is small and only a few of them see the majority of cases, this technique was discouraged because of the risk of missing by chance the most important diagnostic centre.

2.7.3.d *Population proportionate cluster sampling*

To avoid the risk of missing the largest diagnostic centres when drawing the sample at random, a weighted cluster sampling technique was used in some surveys. Based on the list of all diagnostic centres and the number of newly registered patients per year in each, a comprehensive patient population list was compiled. The total number of patients was then divided by 30, the minimum recommended number of clusters to be sampled, and the sampling interval was thus obtained.

The cluster size was calculated by dividing the required sample size by the number of clusters (i.e., 30). From the full list of expected patients, a first patient was randomly picked from within the top sampling interval and then the size of the sampling interval was systematically added, to identify a total of 30 index patients. The centres to which these index patients belonged then enrolled consecutive eligible patients up to the planned cluster size. Large centres could contribute two or more clusters of patients. This technique provides a nationwide representative sample of patients, although the results in a given cluster may not be representative of the district where the diagnostic centre is located.

2.8 COLLECTION OF CLINICAL DATA ON INDIVIDUAL PATIENTS

2.8.1 Patient eligibility and registration

All patients with smear positive tuberculosis and registered for treatment were eligible for this study. They included children (except in Lesotho and Swaziland), foreign-born persons, hospitalised patients, and those with known HIV co-infection. HIV testing was not a systematic component of these surveys. However, countries that performed HIV testing as part of the survey were advised to follow international guidelines on counselling and confidentiality[66].

The majority of patients had smear positive pulmonary disease and were diagnosed in the public sector. In industrialised countries, culture-proven cases were also included regardless of smear result or site of disease. The survey in Portugal initially excluded cases receiving 1 or 2 doses of anti-tuberculosis treatment before cultures were obtained. Almost all surveys included patients with and without previous history of anti-tuberculosis treatment separately; six countries reported only primary drug resistance prevalence. Reports from Australia, India and the Netherlands did not distinguish between primary and acquired resistance, and only combined drug resistance prevalence is presented and analyzed. A minority of patients in the USA and France could not be classified as new or retreatment cases and were excluded (their levels of drug resistance were similar to those of previously untreated cases).

Each patient meeting the inclusion criteria was assigned a serial number in each diagnostic centre, which was recorded on the intake forms (see Annex 1d). Intake forms included demographic data as well as information on prior treatment; individual surveys included questions on HIV status, foreign birth, etc. Radiologic results were not routinely obtained or reported, and are not included in this analysis.

2.8.2 Accuracy of information on prior anti-tuberculosis treatment

Following the WHO/IUATLD Guidelines for surveillance of drug resistance in tuberculosis[46], and with the exception noted above, participating programmes administered a face-to-face questionnaire to ascertain whether drug resistance was primary or acquired. When available, medical records and district registers were also reviewed for evidence of prior treatment. Classification of cases as never treated and previously treated was the essential step for distinguishing between primary and acquired drug resistance.

Special efforts were made to ensure the reliability of clinical data. First of all, clinical interview forms were checked for deficiencies. Second, the reliability of the information recorded was assessed regularly during the survey. In selected surveys where the adequacy of this information was questioned, a representative sample of patients was reinterviewed by the coordinating team. Depending on the accuracy of the results, corrective measures and additional training were implemented. Finally, the Global Project Coordinator at WHO made monitoring visits to selected countries to evaluate how representative the survey cases were, the accuracy of history of prior treatment, and the handling of laboratory specimens.

2.8.3 Data management in individual countries

In order to facilitate data collection and analysis of anti-tuberculosis drug resistance, WHO developed a software programme, based on Epi-Info 5. The programme, Surveillance of Drug Resistance in Tuberculosis (SDRTB), was distributed free of charge to participating countries accompanied by a user's manual. To ensure accuracy in data entry, data were to be entered twice using the "Validate" option in SDRTB. A pre-programmed analysis could be run easily and summary tables with the prevalence of drug resistance for each drug and cumulative drugs produced. Approximately a third of the countries included in this report used the SDRTB software for data collection and preliminary analysis.

At regular intervals during the intake period, coordinating teams tabulated all data produced by the diagnostic centres and the central laboratory. Based on these tables, national coordinators made regular reports to the chiefs of the NTP and the NRL, updating them on patient enrolment, adequacy of clinical information collected, transport or logistical problems, and contamination of specimens. In some of the largest surveys, the national coordinator and the chiefs of the NTP and the NRL met during the course of the survey to discuss the quality of data collection and laboratory procedures, the quality assurance process, and preliminary survey results. Standardised reports were then submitted to WHO GTB Programme for global analysis.

2.9 MYCOBACTERIOLOGICAL METHODS AT COUNTRY LEVEL

Sputum smear microscopy, generally using the Ziehl-Neelsen technique, was performed in most individual diagnostic centres to determine patient eligibility. In addition to the initial sputum sample used for smear microscopy, the diagnostic centres sent to the NRL additional samples from all patients found to be eligible for inclusion. As treatment for some time may reduce the chance of a positive culture[67], sputum samples were to be taken ideally before starting treatment. Copies of the clinical intake form were shipped with the sputum samples to the National Reference Laboratory (NRL). When peripheral

culture laboratories participated in the survey, subcultures instead of sputum samples were submitted to the NRL. In aggregate, over 55,000 patients were enroled by the different surveys or surveillance projects. A median of 95.5% of the samples collected by each study had DST results (Table 4). The other samples either did not yield a culture or were contaminated.

2.9.1 The National Reference Laboratory (NRL)

The NRL, which was the reference institution in each country conducting the survey or surveillance, prepared cultures from the sputum samples and performed strain identification and susceptibility testing as part of the survey. Testing was performed either following the Guidelines or, after agreement with a SRL, following the procedures established nationally. The WHO/IUATLD Guidelines provided specific recommendations for handling and safe transportation of specimens between different geographic locations (Annex 1b)[52,53,54].

Some exceptions to this structure should be noted. In countries with routine surveillance, such as the USA, cultures and DST were performed by numerous regional laboratories under central monitoring and accreditation[68]. In countries without a functioning NRL, such as Lesotho and Swaziland, all survey samples were submitted to the corresponding SRL for testing; in the cases of Sierra Leone, Zimbabwe and Estonia, DST of all samples was performed in both their NRL and the corresponding SRL in Germany and Sweden (the SRL results are presented and analysed).

2.9.2 Culture and identification of *M. tuberculosis*

Before processing at the central tuberculosis laboratory, sputum samples were generally kept in a refrigerator at +4˚C; bacteriological examination was carried out as soon as possible. Samples were decontaminated and further homogenised, according to Petroff's method, with sodium hydroxide 4% at 37˚C, centrifuged at 2000-3000 g for 20 minutes, and the sediment neutralised and washed. Total contact time with sodium hydroxide was not to exceed 30 minutes. Other standardised methods were permitted. Specimens treated with cetylpyridinium chloride/bromide were not required to undergo further decontamination treatment[69].

The sediment was generally inoculated into two tubes of L-J medium and one tube of egg medium enriched with sodium pyruvate. Modifications of the L-J medium, alternative culture media or their combinations were used in a few countries as noted in Table 4. The cultures were incubated at 37˚C for nine weeks or until growth of colonies was observed. They were first inspected after 48 hours and then weekly. If there was no growth by day 63, or if contamination was detected, the cultures were discarded and the laboratory forms completed accordingly. Positive cultures were kept until retesting at the Reference Laboratory was completed or the strain was excluded from further testing. Cultures were stored in a deep freezer at -20˚C, but they could also be kept for some time in a refrigerator at +4˚C, or even at room temperature.

Identification of the strains was based on at least the niacin production test, the nitrate reduction test and the thiophene carboxylic acid hydrazide (2 mg/l) resistance test. Identification using standard DNA probe tests was also acceptable[46, 47]. If colony morphology was consistent with *M. tuberculosis* complex only one culture per patient

needed to be identified. Mycobacteria other than the tubercle bacilli were excluded from analysis.

2.9.3 Anti-tuberculosis drug susceptibility testing and quality assurance

Drug susceptibility was performed in the NRL with laboratory personnel who were blinded to clinical information, especially history of prior treatment. Indirect susceptibility testing was performed only on one isolate from each patient. Drug resistance tests were generally performed using the economic variant of the proportion method on L-J medium[43], although the absolute concentration, resistance ratio, and other standardised methods were also used (Table 4). Resistance to INH, RMP, SM, and EMB was routinely tested if these drugs were used in the tuberculosis programme, prescribed by private practitioners, or otherwise available to the population. In Australia only a third of the specimens were tested for SM resistance, since that drug is only rarely used in that country.

Resistance was expressed as the percentage of colonies that grew on critical concentrations of the drugs, *i.e.,* 0.2 mg/l for INH, 2 mg/l for EMB, 4 mg/l for dihydrostreptomycin sulphate and 40 mg/l for RMP when the L-J medium was used. The interpretation was according to the usual criteria for resistance, *i.e.* 1% for all drugs. The results of the tests were then recorded on standardised laboratory forms (Annex 1), copies of which were collected by each national coordinator and reported to WHO for global analysis using sometimes SDRTB.

To ensure that the results of susceptibility testing were reliable and comparable between different countries, a system of proficiency testing was implemented. The main components of a quality assurance programme were internal quality control of laboratory procedures and an international proficiency testing of DST by the corresponding SRL[47]. The latter consisted of exchanging samples of coded *M. tuberculosis* strains between the SRL and the NRL, and comparing the results of double blinded DST. For the nine countries hosting a SRL and five surveys with all samples tested in the SRL, the gold standard was the judicial result of the SRL network; for the other surveys, the gold standard was the results of the corresponding SRL. This quality assurance exercise was conducted at the beginning of the survey in the majority of the countries. Table 4 lists the number of specimens exchanged and the overall agreement (i.e., results concordance) between NRL and SRL for the four drugs evaluated. A median of 20 strains were exchanged (range, 8 to 510). The overall agreement ranged from 84% to 100%, with a median of 95%; the specificity for RMP DST was under 97% in only five cases. The minimum recommended interlaboratory agreement was 90%. In most cases, significant discrepancies were clarified before implementing the survey.

Table 4. Laboratory methods and performance at each of the NRLs in the Global Project

COUNTRY	CULTURE	DST METHOD*	PT** STRAINS	NRL/SRL** AGREEMENT	Specificity for RMP DST	PATIENTS ENROLLED	% with DST RESULTS
Argentina	Loewenstein-Jensen and others	Proportion method	65	99.6	100.0	894	100
Australia	Loewenstein-Jensen and BACTEC	BACTEC	20	100.0	100.0	705	100
Benin	Loewenstein-Jensen	Proportion method	63	87.0	100.0	409	81
Bolivia	Loewenstein-Jensen	Proportion method	108	91.6	98.8	704	86
Botswana	Loewenstein-Jensen	Resistance ratio method	23	95.6	100.0	521	100
Brazil	Loewenstein-Jensen	Proportion method	59	96.5	100.0	4992	58
China (Henan province)	Loewenstein-Jensen	Absolute concentration method	30	89.0	88.0	2318	
Cuba	Loewenstein-Jensen	Proportion method	20	84.0	80.0	786	100
Czech Republic	Loewenstein-Jensen and others	Proportion method	40	89.4	87.0	239	90
Dominican Republic	Loewenstein-Jensen	Proportion method	25	94.4	100.0	688	61
England & Wales	Loewenstein-Jensen and BACTEC	Resistance ratio method	20	99.0	100.0	2890	100
Estonia	BACTEC	BACTEC	20	97.5	93.5	623	47
France	Loewenstein-Jensen and BACTEC	Proportion method	20			1853	91
India (Delhi state)	Loewenstein-Jensen	Proportion method	20	90.0	100.0	2570	87
Italy	Loewenstein-Jensen	Proportion method	25	97.0	100.0	167	100
Ivory Coast	Loewenstein-Jensen	Proportion method	93	93.9	98.1	429	75
Kenya	Loewenstein-Jensen	Resistance ratio method	95	97.4	99.0	638	77
Latvia	Loewenstein-Jensen	Various	12	93.8	86.0	575	100
Lesotho	Loewenstein-Jensen	Proportion method	20	94.0	100.0	468	82
Nepal	Loewenstein-Jensen	Proportion method	77	95.8	97.3	914	86
Netherlands	Various	Proportion method	20	95.0	100.0	1104	100
New Zealand	BACTEC	BACTEC	20	97.5	100.0	437	100
Northern Ireland	Loewenstein-Jensen and BACTEC	Resistance ratio method	38	100.0	100.0	59	100
Peru	Loewenstein-Jensen	Proportion method	136	96.3	99.2	1958	100
Portugal	Loewenstein-Jensen	Modified Proportion Method	20	98.0	100.0	928	100
Puerto Rico	BACTEC	Proportion method and BACTEC	8	100.0	100.0	420	93
Republic of Korea	Ogawa	Proportion method	20	95.0	100.0	2675	100
Romania	TB-glut and Loewenstein-Jensen	Absolute concentration method	113	90.1	96.8	3443	92
Russia (Ivanovo Oblast)	Loewenstein-Jensen	Proportion method	20	95.0	100.0	290	97
Scotland	BACTEC	BACTEC	20			290	100
Sierra Leone	Loewenstein-Jensen and others	Proportion method	20	95.0	100.0	381	94
Spain (Barcelona)	Loewenstein-Jensen and BACTEC	Proportion method	20	96.0	100.0	262	100
Swaziland	Loewenstein-Jensen	Pproportion method	20	94.0	100.0	407	93
Thailand	Loewenstein-Jensen	Proportion method	30	89.2		150	87
United States of America	Various	Various	20	99.8	99.6	18292	78
Viet Nam	Loewenstein-Jensen	Proportion method	60	92.7	97.0	640	100
Zimbabwe	Ogawa	Various	510	96.7	100.0	712	100

*Drug susceptibility testing (DST): Absolute concentration method used in 4 surveys, 3 of which also used proportion methods. BACTEC was used in 6 surveys, 2 of which also used standard proportion methods. **Number of strains exchanged between NRL and SRL for proficiency testing (PT), and the proportion of results in agreement between the two.

2.10 ECOLOGICAL ANALYSIS OF DRUG RESISTANCE AND NATIONAL TB PROGRAMME CHARACTERISTICS

In order to provide a quantitative interpretation of the observed prevalence of drug resistance in each country, an ecological correlation was performed with characteristics of the corresponding NTP. Ecological analyses compare aggregated or averaged data at group level (e.g. by country) rather than individual subject's results[70,71,72]. Several factors, ascertained through different sources, were considered for this analysis.

2.10.1 Variables included in the ecological analysis

Possible factors associated with the detected level of drug resistance by country were identified including:

2.10.1.a WHO geographical regions

AFR for sub-Saharan Africa, AMR/PAHO for the American continent, EMR for the Eastern Mediterranean countries, EUR for all of Europe, SEAR for South-East Asia, and WPR for the Western Pacific Region.

2.10.1.b Implementation status of the WHO tuberculosis control strategy

The WHO strategy (also referred to as "DOTS") includes the following elements: a) government's commitment to a sustainable NTP; b) case detection among symptomatic patients self-reporting to health services, utilizing sputum-smear microscopy; c) administration of standardised short-course chemotherapy with direct observation of treatment; d) establishment of a system of regular drug supply of all essential anti-tuberculosis drugs; and e) establishment and maintenance of a standardised recording and reporting system allowing assessment of treatment results[63].

Elements of the WHO TB control strategy ("DOTS")

- Government's commitment to a sustainable NTP.
- Case detection among symptomatic patients self-reporting to health services, utilizing sputum-smear microscopy.
- Administration of standardised short-course chemotherapy with direct observation of treatment.
- Establishment of a system of regular drug supply of all essential anti-tuberculosis drugs.
- Establishment and maintenance of a standardised recording and reporting system allowing assessment of treatment results.

In order to monitor a country's progress in implementing the WHO TB control strategy, a classification system, based on a number of indicators, has been developed[63] (see the box below). This analysis does not include small countries and territories not reporting to WHO. The remaining five groups were divided into two categories for

stratified analyses and improved statistical power: countries with poor TB control (i.e. those in categories 1 and 2, and countries in category 3 with ≤33% WHO DOTS coverage), and countries with good TB control (i.e., those in categories 4 and 5, and countries in category 3 with WHO DOTS coverage above the median figure of 33%).

Categorization of countries according to the implementation of WHO TB control strategy

0. Not reporting to WHO on TB control activities.
1. Not accepting WHO TB control strategy and TB notification rate >10/100,000.
2. Implementing WHO TB control strategy in less than 10% of the population.
3. Implementing WHO TB control strategy in 10 to 90% of the population.
4. Implementing WHO TB control strategy in over 90% of the population.
5. Not accepting WHO TB control strategy and TB notification rate <10/100,000.

2.10.1.c *Tuberculosis incidence and several control indicators reported by NTP*

Tuberculosis incidence and several control indicators reported by NTP to WHO Global surveillance system[63]. We explored correlations between prevalence of drug resistance and incidence rate of smear positive TB cases, proportion of estimated sputum smear positive cases that are detected (i.e., the case detection rate), and the proportion of all cases presenting to treatment that are retreatment cases (i.e., failures, return after default, relapses, etc.). In these analyses we also included treatment outcomes, specifically the proportion of cases successfully treated (cure plus treatment completion, as defined in section 2.6.5.)

2.10.1.d *Additional ecological parameters analyzed*

- Estimated prevalence of HIV co-infection among TB patients at country level
- Proportion of cases receiving short course chemotherapy (SCC)
- Use of directly observed therapy
- Year of introduction of RMP to the country
- Use of fix-dose combination (FDC) tablets in tuberculosis treatment, and
- Estimated proportion of cases treated in the private sector

2.10.2 Sources of ecological information

A standardised data collection form with questions on the above variables was sent to all the countries participating in the project (Annex 1f). The information was provided by the coordinating teams of the surveyed countries, including principal investigators and heads of NTPs. The information above was validated from additional sources of information (see below). Inconsistencies were clarified by the reporting investigators.

The official surveillance reports and estimates from WHO were also used to provide data on the incidence of TB and proportion of patients treated successfully. Data were also obtained through reports of recent national TB programme evaluations, when

available, as well as consultations with experts on the TB situation in a specific country.

The computerised compendium of HIV seroprevalence reports compiled by the US Bureau of the Census was consulted to ascertain the proportion of TB patients co-infected with HIV in developing countries[73]. For European countries the quarterly reports of the European Centre for the Epidemiological Monitoring of AIDS were consulted[74]. The reader should keep in mind the difficulty in estimating this parameter as many HIV-coinfected patients are sputum-smear negative and some cases do not even have tuberculosis.

Reports on the use of FDC preparations were reviewed and compared with an independent source, Intercontinental Medical Statistics (IMS), Inc. This London-based company performs annual audits of drug sales in several countries, including a majority of those in the Global Project. IMS provided the proportion of INH standard units (which makes volume comparisons between different dose forms possible, e.g. between syrup and tablets), imported or locally manufactured, that wholesalers sold through private or government-run pharmacies during 1994 and 1995. This information was used to validate the figures reported by principal investigators at country level; significant discrepancies between IMS reports and those of the investigators were discussed with them and an agreement was reached after consulting with additional experts.

2.10.3 Statistical analysis of ecological data

Statistical analyses, including descriptive statistics of the study population and bivariate analyses, were conducted on Epi-Info 6 and SPSS/Windows 7. Central tendency and variance values were calculated for each estimate of drug resistance prevalence - i.e., primary, acquired or combined - for individual drugs and pertinent combinations. In addition to median values, we calculated mean values weighted by the estimated number of smear positive cases in each country or region using SPSS weighing procedure. Ninety-nine percent confidence intervals for this weighted estimate were within 0.1% and are not listed in the tables.

Cross-sectional analyses were performed using the variables described in the previous section (2.10.2) and the outcome parameters described below. Although we lacked statistical power to test interactions formally, we performed stratified analyses across level of TB control as preliminary illustrations for selected contrasts.

The primary dependent or outcome variables in the ecological analysis were:

- proportion of TB cases with any primary drug resistance;
- proportion of TB cases with primary MDR;
- the combined prevalence of resistance to any anti-tuberculosis drug (i.e., primary and acquired) among all patients registered for treatment;
- the acquired MDR index (Section 3.4.4).

All tests of significance were two-tailed and no adjustments were made for multiple comparisons. Categorical data were contrasted using the Mantel-Haenszel chi-square test; when the expected value of a cell was less than 5, Fisher's exact two-tailed test was used. To compare continuous data, the Student's t-test was used for normally distributed variables; otherwise the Wilcoxon two-sample test was chosen. For categorical, ordinal predictors, p-values for trends were obtained with ANOVA. The bivariate association between continuous predictors and drug resistance estimates was evaluated by the Spearman rank correlation (r_s). Scatterplots were generated to illustrate selected correlations.

Several limitations were recognised before performing the ecological analysis. The number and interrelation of causative factors in drug resistance make the analytic strategy complex and multivariate. However, the number of units of analysis was relatively small for that type of approach. The direction of some of the associations is ambiguous; for example, incomplete treatment may facilitate the development of drug resistance, but MDR-TB may also decrease the chances of successful treatment even under expert and committed supervision[19]. Most importantly, the data on drug resistance represented snapshots at single points in time rather than trends, and the lag time between a particular factor and the development of drug resistance is uncertain and may vary. With these constraints in mind, we performed a cross-sectional, ecological analysis. Multivariate regression models could not be fitted.

CHAPTER THREE

RESULTS

3.1 REPRESENTATIVENESS OF THE COUNTRIES IN THE GLOBAL PROJECT ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

Of the 216 WHO countries, areas and territories, 35 (16%) are included in this report, representing all geographical areas except for the Eastern Mediterranean region. Eight (23%) of the surveys were done in African countries, and another 8 (23%) in the Americas. Thirteen reports were from 11 European nations (31%), representing 21% of the countries in that region. Three of the 10 countries (30%) in South-East Asia are included in this report, representing 8.6% of the total reported number in this document. Finally, 5 of the 35 reports (14%) originated in the Western Pacific region (Table 5). Annex 2 presents the profile of the individual countries surveyed.

While 16% of the WHO countries, areas and territories were included in the Global Project, the surveys sampled tuberculosis patients in areas with an aggregate population of 1,142,174,100. This represents grossly 20% of the world's total population in 1995 (Fig. 2). These estimates are based on the population targeted by the surveys. For example, Russia had 147 million inhabitants in 1995 but the survey was restricted to Ivanovo Oblast; thus only the 1.27 million people of Ivanovo Oblast are reported as covered by the Global Project. Table 5 illustrates the proportion of TB patients covered by anti-tuberculosis drug resistance surveys in each WHO region. The population covered in Africa was 19%, while in the Americas (where the 3 most populated countries in the region were surveyed) the proportion was 77%. In South-East Asia only the State of New Delhi was surveyed within India, the most populous country in the region. Europe and the Western Pacific had, respectively, 20% and 15% of their population targeted by the Global Project.

In addition to global geographic distribution, the countries included in this report represented a wide spectrum of TB control programme performances (Table 6). The few areas that did not report their TB control activities to WHO in 1996 did not participate in the Global Project. Ten of the 35 reports (29%) originated in countries implementing the WHO

Table 5. Representativeness of countries in the Global Project by WHO region

WHO REGION	Parameter	Total in region	Survey targets	(%)*
Africa	No of countries	48	8	(17)
	Population	585,604,000	68,085,000	(12)
	TB cases notified	467,126	87,872	(19)
The Americas	No of countries	47	8	(17)
	Population	774,712,000	512,828,000	(66)
	TB cases notified	238,372	185,221	(77)
The Eastern Mediterranean	No of countries	23	0	(0)
	Population	456,418,000	0	(0)
	TB cases notified	149,041	0	(0)
Europe	No of countries	54	11	(21)
	Population	865,789,000	238,891,000	(27)
	TB cases notified	287,726	56,092	(20)
Southeast Asia	No of countries	10	3	(30)
	Population	1,425,978,000	90,709,000	(6)
	TB cases notified	1,380,341	78,215	(6)
Western Pacific	No of countries	34	5	(17)
	Population	1,609,674,000	231,661,000	(14)
	TB cases notified	775,076	116,974	(15)
WORLD	**No of countries**	**216**	**35**	**(16)**
	Population	**5,718,175,000**	**1,142,174,000**	**(20)**
	TB cases notified	**3,297,682**	**524,374**	**(16)**

* Numerators included population or TB cases notified in the whole country or specific regions surveyed (i.e., State of Delhi in India).

Fig. 2. Proportion of countries and world population covered by the Global Project

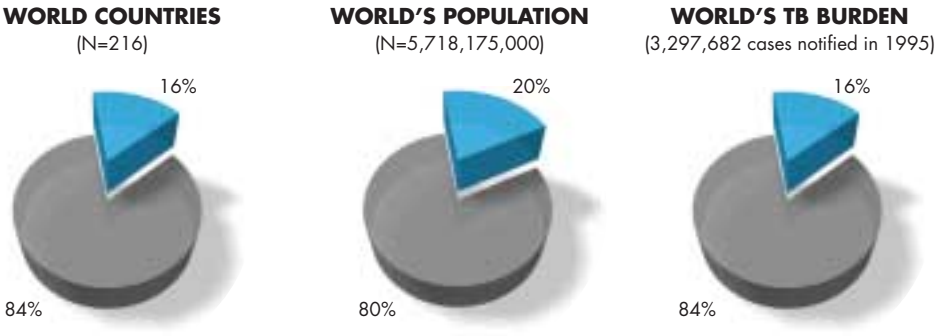


Table 6. Proportion of countries, areas and territories of the world included in this report by WHO TB Control Category

WHO TB Control Category	*Total*	*Global Project (%)*
0. Not reporting to WHO on TB control activities	36	0 (0)
1. Not accepting WHO TB control strategy and TB notification rate >10/100,000	84	12 (14)
2. Implementing WHO TB control strategy in less than 10% of the population	7	2 (29)
3. Implementing WHO TB control strategy in 10 to 90% of the population	29	6 (21)
4. Implementing WHO TB control strategy in over 90% of the population	39	10 (26)
5. Not accepting WHO TB control strategy and TB notification rate <10/100,000	21	5 (24)
TOTAL	216	35 (16)

* Chi-Square P-value .035

strategy in over 90% of their population. Conversely, 12 of the 35 reports analysed (34%) originated in countries not following the WHO strategy and having TB notification rates >10/100,000. Additional reports were from countries in an intermediate phase of implementation of the WHO strategy, as well as from some countries which do not follow it but have already achieved low rates of TB (<10 per 100,000).

While the median population of the 216 countries, areas and territories in the world was estimated at 4,813,500 in 1995, the median population for the 35 countries (or regions) surveyed was 11,005,866. The median number of TB cases notified in 1995 was substantially higher for the countries (or regions) included in the Global Project (5,655) than the world average (2,400). The rate of cases notified or estimated was similar in countries or regions participating in the Global Project and those not surveyed.

3.2 CHARACTERISTICS OF TUBERCULOSIS PATIENTS AND CONTROL PROGRAMMES IN THE COUNTRIES AND REGIONS SURVEYED

In 1995, the countries and regions included in the Global Project notified a median of 5,655 TB cases (range 263 to 88,109). In these countries and regions, a median of 55% of the pulmonary cases were smear positive (range, 18 to 87%). A median of 50% of the population was covered by the WHO TB control strategy in the countries and regions surveyed, ranging from 0 to 100%. The proportion of cases reported as having been treated successfully (i.e., cure plus treatment completion) was 68% (range, 38 to 91%), which is similar to the global reports to WHO. The median proportion of all cases registered for treatment who had previously received anti-tuberculosis treatment was

Table 7. Tuberculosis Control and Surveillance characteristics of the countries and regions in the Global Project on Anti-tuberculosis Drug Resistance Surveillance, 1995.

COUNTRY	WHO Region	Country/region Population	TB cases notified in country/region	Notification rate /100,00	%SS+ in new PTB*	Estimated SS+ cases	WHO TB Control Category **
Argentina	the Americas	34,587,000	13,433	39	55	7,782	1
Australia	Western Pacific	18,088,000	1,073	6		488	5
Benin	Africa	5,409,000	2,400	44	87	3,286	4
Bolivia	the Americas	7,414,000	9,614	130	83	11,177	3
Botswana	Africa	1,487,000	5,655	380	40	2,677	4
Brazil	the Americas	161,790,000	88,109	54	61	58,244	1
China (Henan province)	Western Pacific	91,000,000	39,078	43	43	35,865	3 ***
Cuba	the Americas	11,005,866	1,579	14	65	991	4
Czech Republic	Europe	10,296,000	1,834	18	32	1,158	4
Dominican Republic	the Americas	7,823,000	4,053	52	61	3,872	1
England & Wales	Europe	51,506,127	6,176	11		2,798	1
Estonia	Europe	1,530,000	624	41	75	413	1
France	Europe	57,981,000	8,723	15	54	5,218	1
India (Delhi state)	Southeast Asia	10,000,000	48,600	486	27	41,600	2
Italy	Europe	57,187,000	5,627	10	34	6,434	5
Ivory Coast	Africa	14,253,000	11,988	84	85	12,571	4
Kenya	Africa	28,261,000	28,142	100	59	17,804	3
Latvia	Europe	2,557,000	1,541	60	42	805	1
Lesotho	Africa	2,070,000	4,846	234	34	2,306	4
Nepal	Southeast Asia	21,918,000	19,804	90	52	16,471	2
Netherlands	Europe	15,503,000	1,619	10		907	4
New Zealand	Western Pacific	3,575,000	307	9	18	161	5
Northern Ireland	Europe	1,640,000	75	5	43	89	5
Peru	the Americas	23,780,000	46,787	197	80	26,753	4
Portugal	Europe	9,823,000	5,577	57	60	2,652	4
Puerto Rico	the Americas	3,674,000	263	7	54	132	5
Republic of Korea	Western Pacific	44,453,000	33,196	81	37	32,406	3
Romania	Europe	22,835,000	23,271	102	56	12,331	1
Russia (Ivanovo Oblast)	Europe	1,271,100	662	52	47	566	1 #
Scotland	Europe	5,210,000	6,176	11		281	1
Sierra Leone	Africa	4,509,000	1,914	42	81	3,389	3
Spain (Barcelona)	Europe	1,650,000	961	58	30	364	1
Swaziland	Africa	861,600	2,055	239	49	1,660	1
Thailand	Southeast Asia	58,791,000	45,428	77	47	45,769	1
United States of America	the Americas	262,755,000	22,860	9	43	11,824	5
Viet Nam	Western Pacific	74,545,000	55,739	75	82	55,685	3
Zimbabwe	Africa	11,261,000	30,831	274	36	10,490	4

* Smear positive cases among new cases of pulmonary TB. ** 1. Not accepting WHO TB control strategy and TB notification rate >10/100,000; 2. Implementing WHO TB control strategy in less than 10% of the population; 3. Implementing WHO TB control strategy in 10 to 90% of the population; 4. Implementing WHO TB control strategy in over 90% of the population; 5. Not accepting WHO TB control strategy and TB notification rate of <10/100,000. *** The reported category refers to China as a whole. The Province surveyed is not implementing the WHO strategy. # The reported category refers to Russia as a whole. The Oblast surveyed began to implement the WHO strategy in late 1995.

Table 8. Characteristics and treatment outcomes of tuberculosis patients in the countries and regions surveyed, 1995

COUNTRY	*Estimated HIV (co-infection %)*	*Treatment success (%)*	*Cases for retreatment (%)*
Argentina	8.0	60	19
Australia	4.0		9
Benin	13.0	75	10
Bolivia	3.1	64	25
Botswana	50.0	72	10
Brazil	10.0	54	8
China (Henan province)	0.0	91	30
Cuba	1.3	91	7
Czech Republic	0.0	73	3
Dominican Republic	10.0	71	16
England & Wales	3.0	65	9
Estonia	0.0	65	17
France	12.0	65	10
India (Delhi state)	1.0	83	27
Italy	8.0	80	4
Ivory Coast	45.0	67	6
Kenya	30.0	73	20
Latvia	0.0	55	19
Lesotho	27.0	56	6
Nepal	0.7	73	8
Netherlands	10.0	81	7
New Zealand	6.0		3
Northern Ireland	0.0	65	9
Peru	0.4	81	15
Portugal	6.7	75	12
Puerto Rico	18.0	51	6
Republic of Korea	0.0	81	6
Romania	1.0	38	7
Russia (Ivanovo Oblast)	0.0	70	14
Scotland	2.0	65	4
Sierra Leone	4.5	76	27
Spain (Barcelona)	28.0	65	9
Swaziland	35.0		13
Thailand	20.0	58	3
United States of America	9.0	75	7
Viet Nam	1.2	88	11
Zimbabwe	60.0	67	7

9.3% (range 3 to 30%). The median seroprevalence of HIV co-infection among TB patients was 6%, ranging from 0 (Eastern Europe) to 60% (Zimbabwe). See Tables 7 and 8.

While a few industrialised countries lacked a formal NTP, most of the countries included in this report had one established before 1970, the date of establishment ranging from 1950 to 1995. All countries in the Global Project recommended standardised regimens to treat new patients with tuberculosis. Most of the countries and regions reported some treatment of tuberculosis patients in the private sector. In 14 countries (39%), both industrialised and developing, more than 15% of

Table 9. TB control strategies in the countries and regions surveyed

COUNTRY	NTP* Established	RMP Intro-duction	Treatment in private sector**	Use of SCC (%)	DOT***	Use of FDC tablets (%)****
Argentina	1960	1974	1	100	2	23
Australia	1950	1969	2	96	2	0
Benin	1983	1983	0	100	1	100
Bolivia	1956	1988	2	65	1	60
Botswana	1975	1986	1	100	3	0
Brazil	1964	1979	1	100	0	100
China (Henan province)	1991	1972	2	11	2	20
Cuba	1962	1982	0	100	3	0
Czech Republic	1982	1980	2	75	3	0
Dominican Republic	1985	1979	2	60	0	85
England & Wales	No NTP	1969	0	100	0	67
Estonia	No NTP	1976	0	0	1	0
France	No NTP	1967	2	100	1	20
India (Delhi state)	1962	1982	2	40	0	
Italy	No NTP	1968	1	30	0	25
Ivory Coast	1985	1985	1	100	0	90
Kenya	1956	1993	1	60	1	50
Latvia	1960	1970	0	70	1	5
Lesotho	1986	1980	0	100	1	100
Nepal	1965	1990	2	60	0	0
Netherlands	1955	1965	1	100	0	0
New Zealand	1950	1969	1	96	2	99
Northern Ireland	No NTP	1967	1	90	0	
Peru	1990	1980	1	100	3	20
Portugal	1977	1968	1	60	1	80
Puerto Rico	1953	1981	2	90	0	0
Republic of Korea	1962	1984	2	96	0	0
Romania	1995	1975	0	80	1	0
Russia (Ivanovo Oblast)	1995	1987	0	100	3	100
Scotland	No NTP	1975	0	100	0	100
Sierra Leone	1990	1985	2	70	1	95
Spain (Barcelona)	1982	1968	1	70	2	50
Swaziland	1990	1980	2	100	2	20
Thailand	1966	1985		100	0	20
United States of America	1953	1971	2	95	2	3
Viet Nam	1957	1976	1	67	1	67
Zimbabwe	1959	1990	0	100	1	0

* National tuberculosis program. ** TB Patients treated in the private sector: 0, Virtually all patients treated in the public sector; 1, 0 to 15% of patients treated in the private sector; 2, More than 15% of patients treated in the private sector.
*** Implementation of directly observed therapy: 0, virtually none; 1, initial phase of treatment only; 2, full regimen (<50% of patients); 3, full regimen (>50% of patients). **** Proportion of INH used in fix-dose combination (FDC) tablets with other anti-tuberculosis drugs.

tuberculosis patients were reported as being treated in the private sector (see Table 9).

SCC regimens were reportedly used in a median of 95% of the patients in the countries and regions surveyed (range, 0 to 100%). RMP was introduced by 1990 in most of the countries surveyed, ranging from 1965 (the Netherlands) to 1993 (Kenya). The frequency of the use of drugs in FDC ranged from 0 to 100%, with a median of 20% in the

countries and regions surveyed. Information on actual implementation of directly observed therapy is limited in most countries: of the 35 countries and regions in the survey, 11 (31%) stated directly observed therapy was not used at all, and 12 (34%) only used it during the initial phase of treatment. Thirteen of these countries (37%) stated that they used this strategy throughout the full duration of anti-tuberculosis treatment, but less than half did it for more than 50% of patients they treated. The earliest year of introduction of directly observed therapy was 1971 (Cuba), 1990 being the median year for all countries and regions in the Global Project (Table 9).

3.3 STANDARDIZATION OF SUSCEPTIBILITY TESTING ACROSS THE SUPRANATIONAL REFERENCE LABORATORY NETWORK

One of the crucial requirements to enable the Global Project on Anti-tuberculosis Drug Resistance Surveillance to obtain comparable results on the prevalence of resistance was to ascertain the accuracy of the susceptibility test procedures used in different laboratories across the world. The coordinating laboratory in Canada to date has completed and analysed three rounds of reference strain exchanges. Blind testing was performed at each of the SRLs to ascertain the accuracy and reliability of DST compared to a gold standard that was the judicial result given by the majority of the laboratories[47].

Strain exchange exercises started in late 1994 with the 16 initial SRLs, and were repeated within the network in July 1995 and March 1996 on 20 participating SRLs throughout the world. The results of these exercises are shown in Table 10. The first round of proficiency testing showed that, in general, specificity (the ability to detect drug susceptibility) was better than sensitivity (the ability to detect resistance). The testing of INH and RMP resistance, the two resistance markers that define MDR-TB, showed the highest degree of efficiency within the SRL network. The results of proficiency testing in rounds 2 and 3 showed sustained accuracy of the DST for INH and RMP while improving the performance of SM and EMB susceptibility testing. This improvement in performance was correlated with a realignment of critical drug concentrations around those recommended in the original descriptions in the Methods section.

Figure 3 depicts the accuracy and reproducibility of DST for all 4 anti-tuberculosis drugs evaluated by the network of SRLs in rounds 1, 2, and 3. DST specificity was high in round 1 and was over 95% in the third round. Sensitivity of DST was 87% in round 1 but steadily improved to 96% in the second and third round of proficiency testing. The overall efficiency (i.e., the proportion of results in agreement) was consistently high over the three proficiency testing rounds. The average intralaboratory reproducibility (i.e., consistency of DST results in the two identical sets of 10 strains tested) was 93% in the first round and steadily increased to reach 97% in the last round of proficiency testing. Figure 4 shows how the relatively poor initial sensitivity of DST across SRLs was due to deficiencies in testing for EMB and SM resistance, and the improvements in the two subsequent rounds of proficiency testing: the sensitivity of EMB DST increased from 66% in the first round to 90% in the last round.

In summary, the specificity of DST across the SRL network for all 4 anti-tuberculosis drugs evaluated was very good, and was 100% for INH and RMP. These results for DST were quite homogeneous despite the different methodologies used by laboratories around the world. More importantly, these results predict a very low rate of false positive drug resistance results and protect against overestimating the true prevalence of drug resistance in population surveys. The sensitivity of DST by the SRLs was also

Table 10. Results of proficiency testing in the Global Network of Supranational Reference Laboratories

*Accuracy measure (%)**	*INH*	*RMP*	*EMB*	*SM*	*Overall*
Sensitivity					
1994	99	94	66	88	87
1995	94	99	75	92	93
1996	97	98	90	96	96
p-value:	0.264	0.218	0.123	0.271	0.058
Specificity					
1994	100	96	98	100	99
1995	86	99	84	82	86
1996	100	100	96	91	96
p-value:	0.001	0.065	0.0001	0.012	0.0001
Efficiency					
1994	99	96	91	92	95
1995	93	99	81	90	91
1996	98	99	94	93	96
p-value:	0.004	0.085	0.0002	0.833	0.008
Reproducibility					
1994	98	94	93	89	93
1995	98	99	90	97	96
1996	98	98	99	92	97
p-value:	0.921	0.135	0.054	0.170	0.163

* Definitions: *sensitivity*, ability to detect true resistance; *specificity*, ability to detect true susceptibility; *efficiency* (or overall accuracy), the number of correct results divided by the total number of results; and intralaboratory *reproducibility* (or reliability) between duplicate cultures expressed as percent agreement. **p-values were obtained with ANOVA for the mean values in all SRLs.

excellent for INH and RMP. For EMB and SM, results in 1994 revealed low sensitivity values, but the performance of SRLs improved over time. Thus, in early surveys, the prevalence of resistance to EMB may represent an underestimate. This quality assurance programme has demonstrated that reliable DST results can be obtained and compared internationally[47].

The overall pattern was similar for the accuracy of the NRLs directly involved in the surveys. Specificity was generally high for all 4 drugs evaluated, as was the sensitivity of DST for INH and RMP. The sensitivity of DST for SM and EMB was relatively low in the early surveys, but improved over time in NRLs as it did in the SRL network. The efficiency or overall agreement for the 4 drugs evaluated for each country is presented in Table 4; specificity of RMP DST (which prevents false positive MDR results) was excellent, with values greater than 97% in 80% of the reference laboratories.

Fig. 3. Accuracy and reliability of DST for all 4 anti-tuberculosis drugs combined as performed by the SRLs

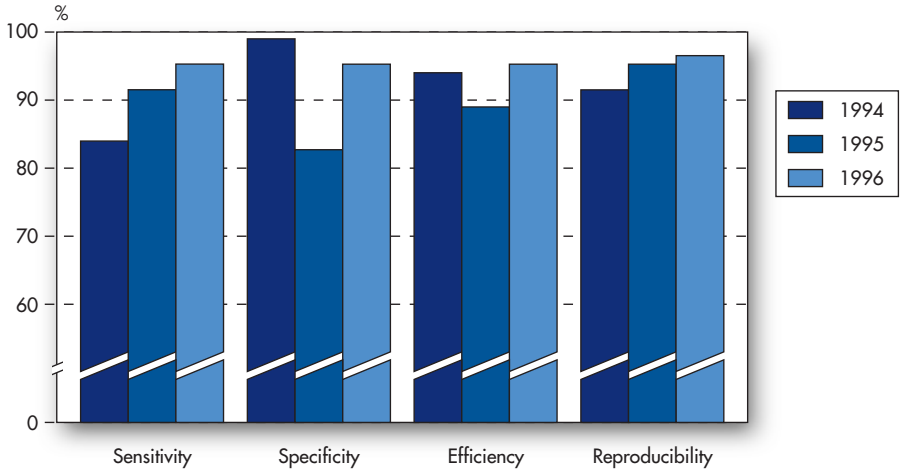
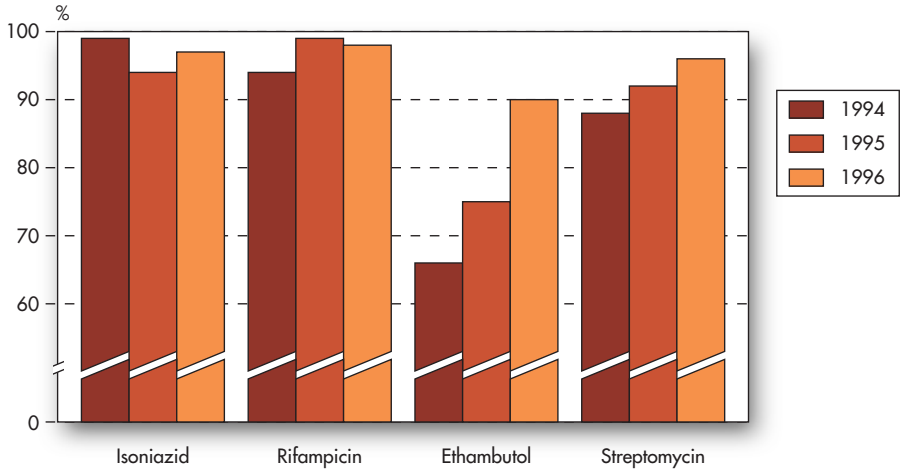


Fig. 4. Average sensitivity of DST for each drug by the Global Network of SRLs



3.4 PREVALENCE OF ANTI-TUBERCULOSIS DRUG RESISTANCE

3.4.1 Primary drug resistance

The results of primary drug resistance in the 32 countries providing this information are shown in Tables 11 and 12. The prevalence of resistance to any drug among patients

Table 11. Prevalence of Primary Drug Resistance to each drug by Country, 1994-1997

COUNTRY	*Patients tested*	*INH*		*RMP*		*EMB*		*SM*	
		mono	*any*	*mono*	*any*	*mono*	*any*	*mono*	*any*
Argentina	606	2.0	7.8	0.3	5.1	0.2	3.1	4.1	7.6
Australia	*								
Benin	333	3.3	5.4	0.0	0.3	0.0	0.6	2.7	4.8
Bolivia	498	6.8	10.2	2.8	6.0	3.6	5.0	6.8	9.8
Botswana	407	1.2	1.5	0.7	1.0	0.0	0.0	1.5	1.5
Brazil	2,095	3.8	5.9	0.2	1.1	0.1	0.1	2.4	3.6
Cuba	763	1.0	2.0	0.1	0.9	0.0	0.0	6.0	6.9
Czech Republic	199	1.0	2.0	0.0	1.0	0.0	1.0	0.0	1.0
Dominican Republic	303	8.6	19.8	6.9	16.2	0.3	3.6	9.9	21.1
England & Wales	2,742	3.3	5.5	0.2	1.2	0.0	0.3	1.1	2.5
Estonia	266	4.1	21.1	0.0	10.2	0.8	7.1	6.4	21.1
France	1,491	0.8	3.4	0.2	0.7	0.1	0.3	4.5	7.0
India (Delhi state)	*								
Ivory Coast	320	3.1	11.3	0.0	5.3	0.0	0.3	2.2	6.9
Kenya	445	5.4	6.3	0.0	0.0	0.0	0.0	0.0	0.9
Latvia	347	5.5	31.7	0.0	14.7	0.0	4.9	2.0	28.0
Lesotho	330	5.2	7.9	0.0	0.9	0.0	0.0	0.9	3.0
Nepal	787	1.7	5.6	0.4	1.7	0.0	1.1	3.7	7.4
Netherlands	*								
New Zealand	418	3.1	4.3	0.0	0.7	0.0	0.5	0.5	1.0
Northern Ireland	59	0.0	1.7	0.0	1.7	0.0	0.0	1.7	1.7
Peru	1,500	3.1	7.5	1.5	4.6	0.4	1.6	5.1	8.7
Portugal	815	1.8	7.1	0.0	1.8	0.0	0.2	6.5	11.7
Puerto Rico	369	4.1	6.8	0.5	2.7	1.4	3.0	1.1	2.4
Republic of Korea	2,486	4.5	7.7	0.3	2.2	0.5	2.6	1.5	2.7
Romania	1,636	3.2	7.4	0.5	3.4	1.7	1.7	0.0	3.3
Russia (Ivanovo Oblast)	248	1.2	12.9	0.4	5.2	0.0	6.5	13.7	26.6
Scotland	290	2.4	2.8	0.0	0.3	0.0	0.3	0.0	0.3
Sierra Leone	463	2.6	13.0	0.2	1.3	0.6	2.4	13.0	24.0
Spain (Barcelona)	218	2.3	3.2	0.5	0.9	1.8	1.8	4.1	4.6
Swaziland	334	3.9	9.0	0.0	0.9	0.3	0.9	2.4	7.2
Thailand **	131	4.6	11.5	6.9	16.8	2.3	9.9	7.6	18.3
United States of America	13,511	4.0	7.8	0.6	2.4	0.5	2.0	3.0	6.2
Viet Nam **	640	6.7	20.0	1.1	3.6	0.2	1.1	11.1	24.1
Zimbabwe	676	1.3	3.3	0.0	1.9	0.0	0.6	0.0	0.7
MEDIAN	431.5	3.2	7.3	0.2	1.8	0.3	1.0	2.5	6.5
minimum	59	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.3
maximum	13,511	8.6	31.7	6.9	16.8	3.6	9.9	13.7	28.0
WEIGHTED MEAN***	1,511.4	4.2	9.8	1.5	4.6	0.6	2.4	4.8	10.1

* Only combined data reported. ** These results are preliminary; definite data will be available at the completion of the survey.
*** Arithmetic mean weighted by the estimated number of smear-positive cases of tuberculosis in 1995 for the country or region surveyed.

without history of prior anti-tuberculosis treatment ranged from 2% (Czech Republic) to 41% (Dominican Republic), with a median value of 10.4%. These results are illustrated in Figure 5 and Maps 3a and 3b. Primary resistance to INH ranged from 1.5% (Botswana) to 32% (Latvia), with a median value of 7.3%. Primary resistance to SM was also common (median prevalence 6.5%), ranging from 0.3 (Scotland) to 28% (Latria). Primary resistance

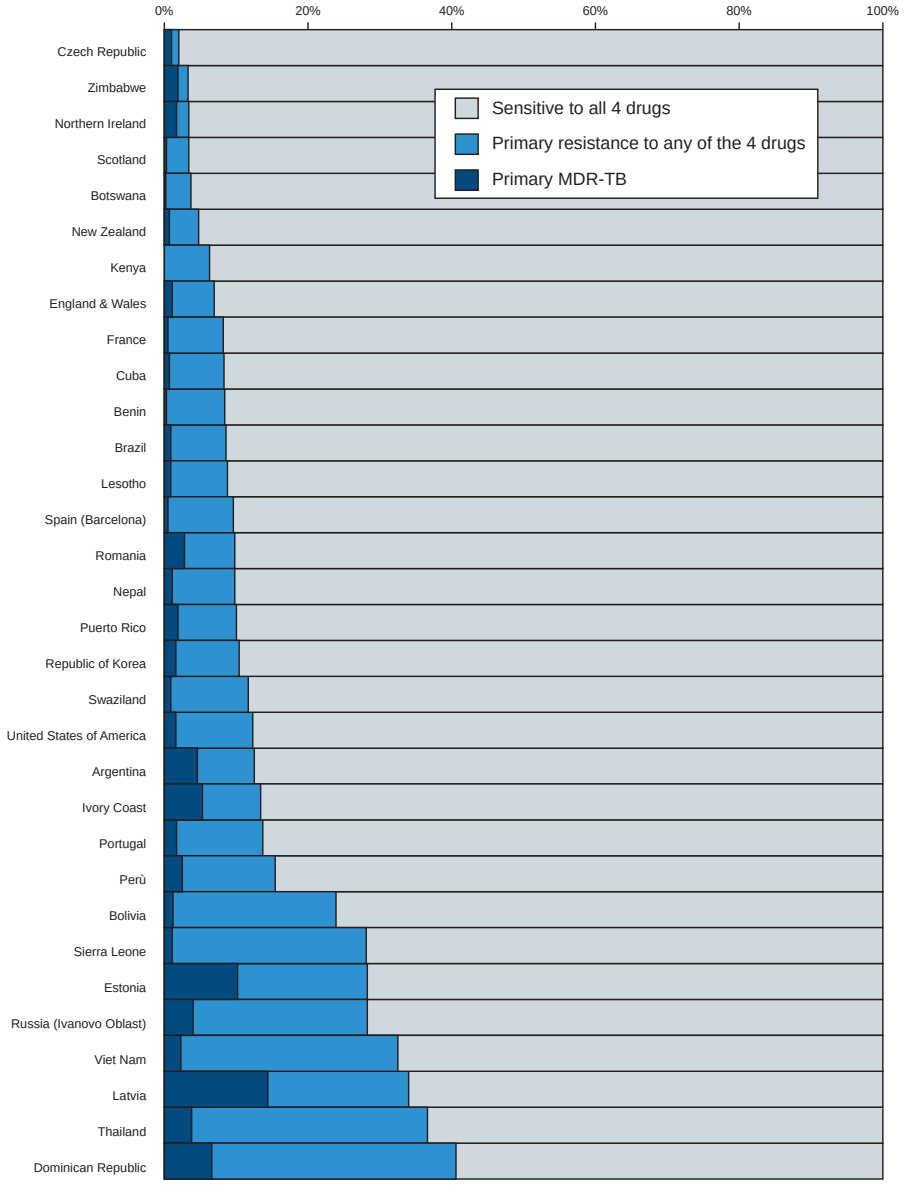
Table 12. Prevalence of Primary Drug Resistance by Country, 1994-1997

COUNTRY	Patients tested	OVERALL		RESISTANCE TO:				POLY-RESISTANCE	
		Suscept.	Resist.	1 Drug	2 Drugs	3 Drugs	4 Drugs	any	MDR
Argentina	606	87.5	12.5	6.6	2.5	1.8	1.7	5.9	4.6
Australia	*								
Benin	333	91.6	8.4	6.0	2.1	0.3	0.0	2.4	0.3
Bolivia	498	76.1	23.9	20.1	5.2	0.2	0.0	5.4	1.2
Botswana	407	96.3	3.7	3.4	0.2	0.0	0.0	0.2	0.2
Brazil	2,095	91.4	8.6	6.4	2.1	0.0	0.0	2.1	0.9
Cuba	763	91.7	8.3	7.2	0.5	0.5	0.0	1.0	0.7
Czech Republic	199	98.0	2.0	1.0	0.0	0.0	1.0	1.0	1.0
Dominican Republic	303	59.4	40.6	25.7	10.9	2.6	1.3	14.9	6.6
England & Wales	2,742	93.1	6.9	4.6	1.9	0.4	0.0	2.3	1.1
Estonia	266	71.8	28.2	11.3	7.1	5.3	4.5	16.9	10.2
France	1,491	91.8	8.2	5.6	2.1	0.5	0.1	2.6	0.5
India (Delhi state)	*								
Ivory Coast	320	86.6	13.4	5.3	6.3	1.6	0.3	8.1	5.3
Kenya	445	93.7	6.3	5.4	0.9	0.0	0.0	0.9	0.0
Latvia	347	66.0	34.0	7.5	12.4	9.5	4.6	26.5	14.4
Lesotho	330	91.2	8.8	6.1	2.4	0.3	0.0	2.7	0.9
Nepal	787	90.2	9.8	5.7	2.8	0.6	0.6	4.1	1.1
Netherlands	*								
New Zealand	418	95.2	4.8	3.6	0.7	0.5	0.0	1.2	0.7
Northern Ireland	59	96.6	3.4	1.7	1.7	0.0	0.0	1.7	1.7
Peru	1,500	84.6	15.4	10.1	3.9	1.0	0.4	5.3	2.5
Portugal	815	86.3	13.7	8.3	3.9	1.2	0.2	5.4	1.7
Puerto Rico	369	90.0	10.0	7.0	1.4	1.4	0.3	3.0	1.9
Republic of Korea	2,486	89.6	10.4	6.9	2.3	1.0	0.2	3.5	1.6
Romania	1,636	90.2	9.8	5.3	2.6	1.7	0.0	4.3	2.8
Russia (Ivanovo Oblast)	248	71.8	28.2	15.3	6.5	2.8	3.6	12.9	4.0
Scotland	290	96.6	3.4	2.4	0.0	0.0	0.3	0.3	0.3
Sierra Leone	463	71.9	28.1	16.6	10.2	1.1	0.2	11.4	1.1
Spain (Barcelona)	218	90.4	9.6	8.7	0.9	0.0	0.0	0.9	0.5
Swaziland	334	88.3	11.7	6.6	3.9	1.2	0.0	5.1	0.9
Thailand **	131	63.4	36.6	21.4	11.5	3.1	0.8	15.3	3.8
United States of America	13,511	87.7	12.3	8.2	2.8	0.7	0.6	4.1	1.6
Viet Nam **	640	67.5	32.5	19.1	11.6	0.9	0.9	13.4	2.3
Zimbabwe	676	96.7	3.3	1.3	1.2	0.1	0.6	1.9	1.9
MEDIAN	431.5	90.1	9.9	6.6	2.5	0.6	0.2	3.8	1.4
minimum	59	59.4	2.0	1.0	0.0	0.0	0.0	0.2	0.0
maximum	13,511	98.0	40.6	25.7	12.4	9.5	4.6	26.5	14.4
WEIGHTED MEAN***	1,511.4	82.0	18.0	11.1	5.4	1.0	0.5	6.9	2.1

* Only combined data reported. ** These results are preliminary; definite data will be available at the completion of the survey.
*** Arithmetic mean weighted by the estimated number of smear-positive cases of TB in 1995 for the country or region surveyed.

to EMB or RMP was much less common. Primary monoresistance to RMP was reported by most countries where the drug had been in use for over a decade, with prevalence ranging from 0% to 6.9% (Dominican Republic), and a median value of 0.2%.

Fig. 5. Prevalence of primary drug resistance to any drug and MDR-TB, 1994-1997



The median prevalence of primary MDR-TB was 1.4%, with a range between 0 (Kenya) and 14.4% (Latvia) (Figures 5 and 6). The average proportion of previously untreated cases with resistance to one (i.e., any monoresistance), two, three or all four drugs is also noted at the bottom of Table 12, and their relative prevalence in the countries studied is illustrated in Figure 7. Primary resistance to all 4 drugs combined was found in a median of 0.2% of the cases (range 0 to 4.6%).

Fig. 6. Prevalence of primary drug resistance in 32 countries and regions, 1994-1997

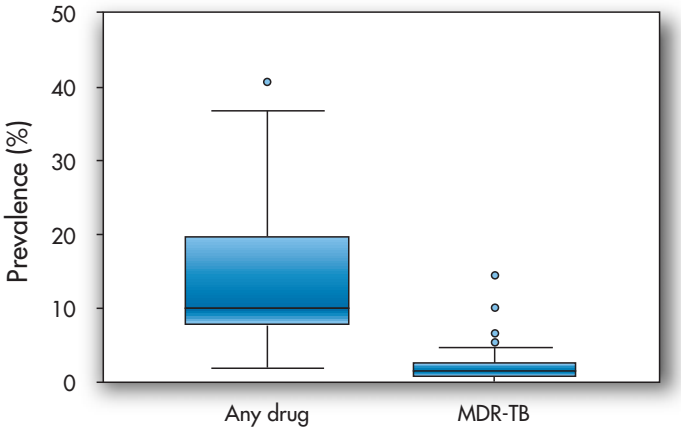
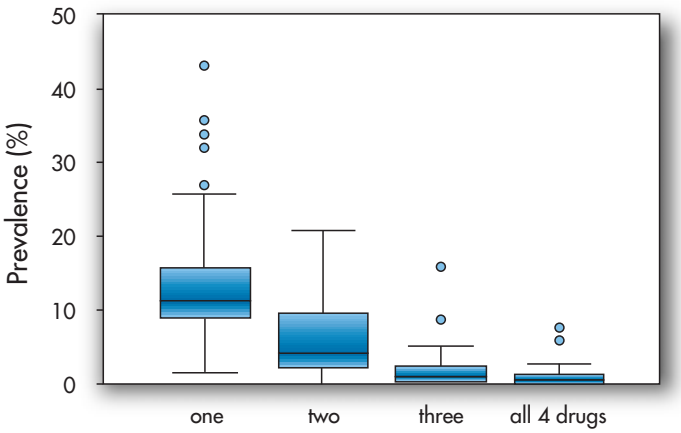
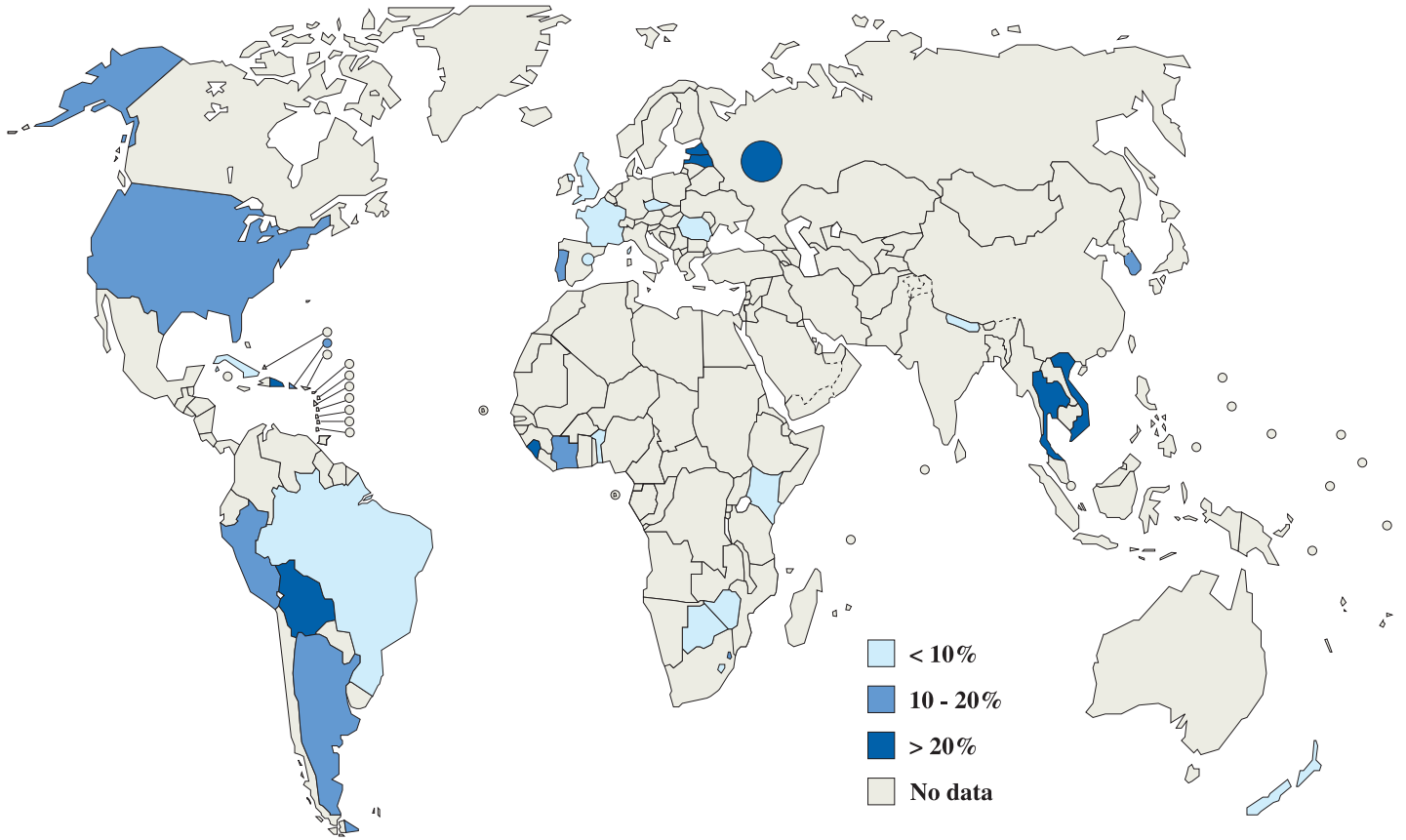


Fig. 7. Prevalence of primary drug resistance to 1, 2, 3 or to all 4 first-line anti-tuberculosis drugs



In each boxplot, the horizontal line accross each box represents the median value, and the bottom and top of the box are the 25th and 75th percentiles; the whiskers are 1.5 times the interquartile range, and outliers are noted individually.

Map 3a. Prevalence of primary resistance to any of the 4 anti-tuberculosis drugs in countries and regions surveyed, 1994-1997



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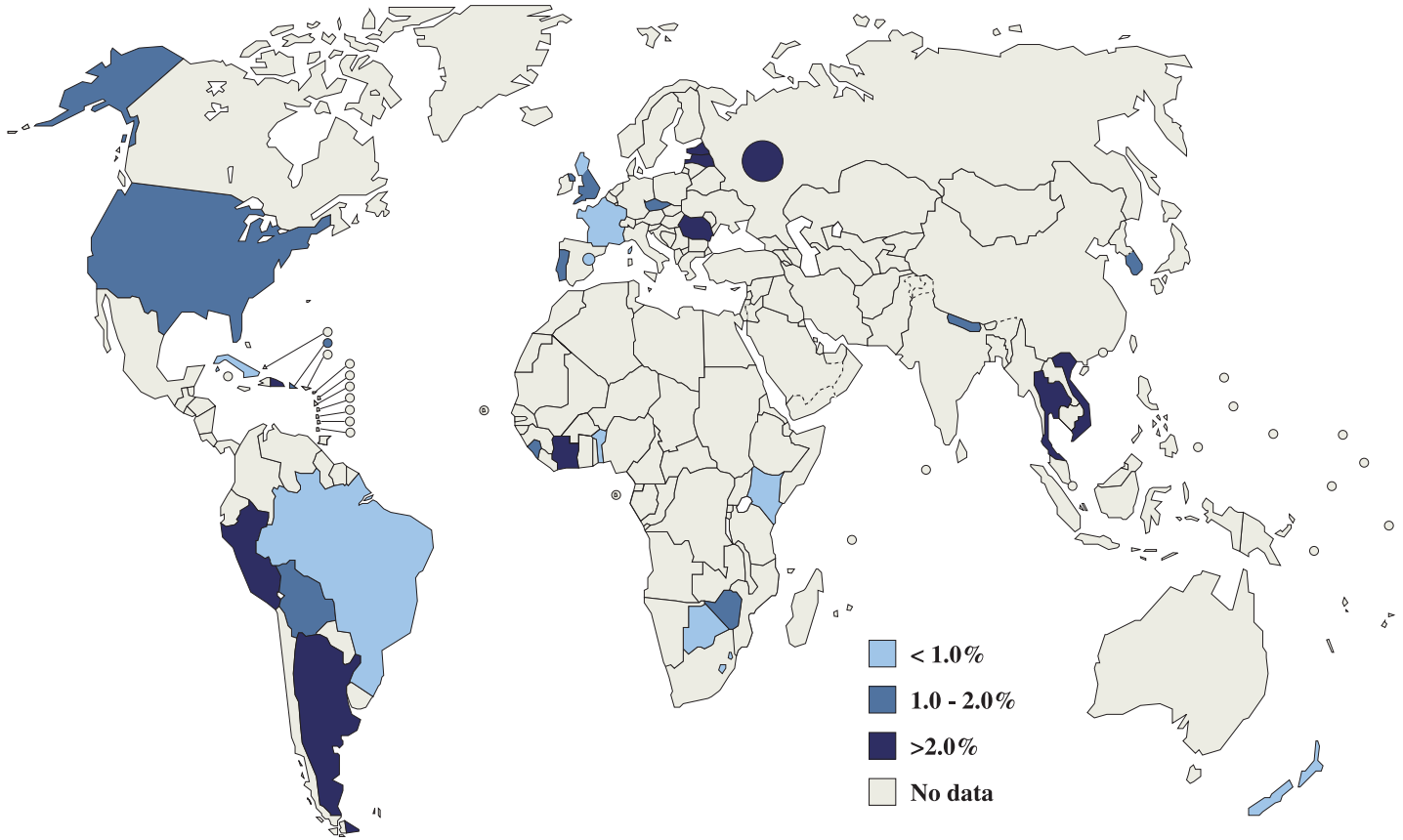
Map 3b. Prevalence of primary MDR-TB in countries and regions surveyed, 1994-1997



3.4.2 Acquired drug resistance

As expected, the prevalence of drug resistance among previously treated patients was much higher than primary drug resistance. An exception to this rule was noted in New Zealand, where only 19 previously treated cases were reported, none of them with MDR-TB. Tables 13 and 14 provide estimates for each of the drugs tested and their combination in each of the 25 countries providing these data (7 surveys reported on new

Table 13. Prevalence of Acquired Drug Resistance to each drug by Country, 1994-1997

COUNTRY	*Patients tested*	*INH*		*RMP*		*EMB*		*SM*	
		mono	*any*	*mono*	*any*	*mono*	*any*	*mono*	*any*
Argentina	288	6.3	32.6	2.1	26.7	0.3	13.9	3.5	25.0
Australia	*								
Benin	**								
Bolivia	107	3.7	10.3	12.1	18.7	4.7	7.5	12.1	15.0
Botswana	114	3.5	10.5	0.9	7.9	0.0	5.3	2.6	8.8
Brazil	793	4.2	11.2	0.6	6.1	0.1	0.3	2.4	5.4
Cuba	23	8.7	30.4	0.0	17.4	0.0	0.0	56.5	82.6
Czech Republic	16	6.3	12.5	0.0	6.3	0.0	6.3	0.0	6.3
Dominican Republic	117	10.3	36.8	8.5	31.6	0.0	12.8	3.4	25.6
England & Wales	148	9.5	29.7	0.7	17.6	0.0	4.1	2.0	9.5
Estonia	26	7.7	46.2	0.0	19.2	0.0	19.2	0.0	38.5
France	195	4.6	13.8	2.6	6.7	0.0	2.1	5.1	11.8
India (Delhi state)	*								
Ivory Coast	**								
Kenya	46	30.4	37.0	0.0	0.0	0.0	0.0	0.0	6.5
Latvia	228	2.6	69.7	1.8	57.9	0.0	18.0	0.4	64.9
Lesotho	53	17.0	30.2	0.0	5.7	0.0	3.8	3.8	17.0
Nepal	**								
Netherlands	*								
New Zealand	19	5.3	5.3	0.0	0.0	0.0	0.0	0.0	0.0
Northern Ireland	**								
Peru	458	5.0	23.8	3.5	20.3	0.7	6.1	7.0	17.2
Portugal	117	4.3	29.9	0.0	18.8	0.0	6.8	7.7	27.4
Puerto Rico	22	4.5	22.7	0.0	18.2	0.0	13.6	0.0	9.1
Republic of Korea	189	10.1	45.5	1.6	32.3	1.1	29.6	1.6	14.8
Romania	1,521	12.4	31.6	1.6	16.4	2.7	2.7	0.0	14.3
Russia (Ivanovo Oblast)	33	15.2	54.5	15.2	54.5	6.1	27.3	9.1	48.5
Scotland	**								
Sierra Leone	172	7.6	43.0	0.6	15.0	0.0	8.7	8.1	42.0
Spain (Barcelona)	44	6.8	27.3	0.0	20.5	0.0	6.8	2.3	18.2
Swaziland	44	2.3	13.6	0.0	9.1	0.0	4.5	6.8	15.9
Thailand	**								
United States of America	833	7.2	18.0	1.0	8.4	0.7	4.7	3.6	11.0
Viet Nam	**								
Zimbabwe	36	5.6	13.9	0.0	8.3	0.0	0.0	0.0	2.8
MEDIAN	114.0	6.3	29.7	0.6	17.4	0.0	6.1	2.6	15.0
minimum	16	2.3	5.3	0.0	0.0	0.0	0.0	0.0	0.0
maximum	1,521	30.4	69.7	15.2	57.9	6.1	29.6	56.5	82.6
WEIGHTED MEAN***	465.0	8.5	24.5	2.0	14.8	0.7	7.4	3.5	12.6

* Only combined drug resistance data reported. **Only primary drug resistance data reported.

*** Arithmetic mean weighted by the estimated number of smear-positive cases of tuberculosis in 1995 for the country or region surveyed.

patients only and 3 others presented combined data only). The prevalence of acquired resistance to any drug ranged from 5.3% (New Zealand) to 100% (Ivanovo Oblast, Russia), with a median value of 36%. These results are shown graphically in Figure 8 and in Maps 4a and 4b.

Table 14. Prevalence and patterns of Acquired Drug Resistance by Country, 1994-1997

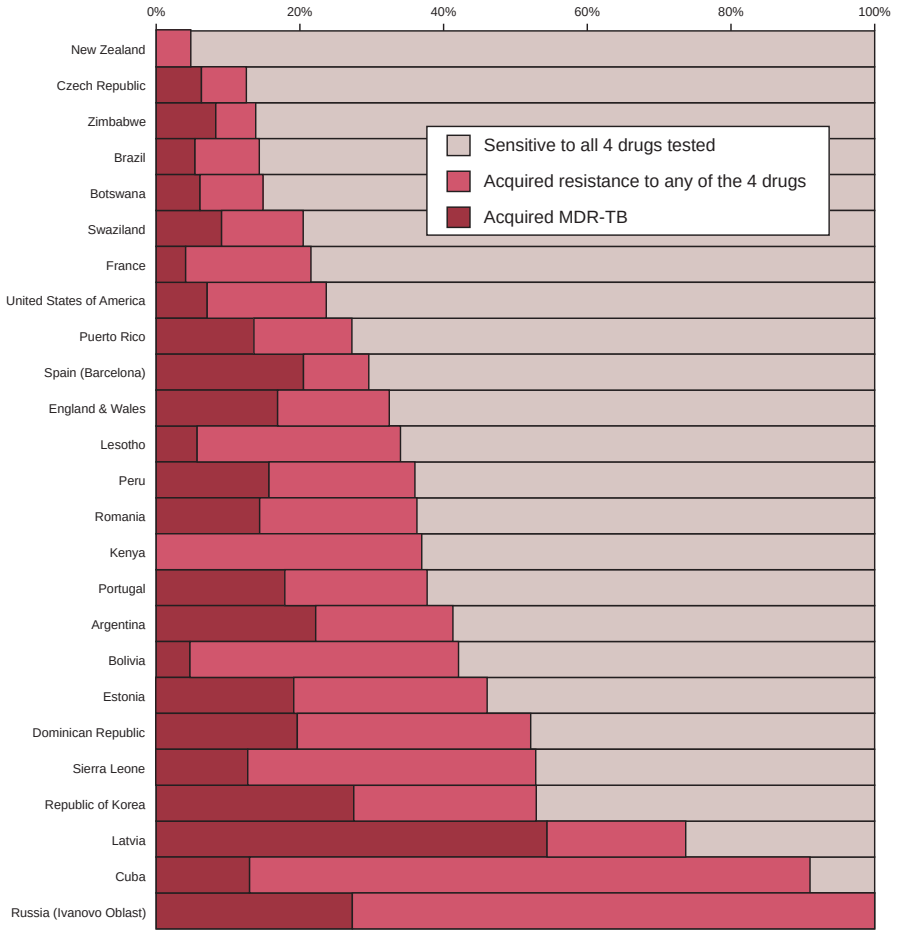
COUNTRY	Patients tested	OVERALL		RESISTANCE TO:				POLY-RESISTANCE	
		Suscept.	Resist.	1 Drug	2 Drugs	3 Drugs	4 Drugs	any	MDR
Argentina	288	58.7	41.3	12.2	9.7	11.1	8.3	29.2	22.2
Australia	*								
Benin	**								
Bolivia	107	57.9	42.1	32.7	7.5	0.0	0.9	8.4	4.7
Botswana	114	85.1	14.9	7.0	2.6	0.9	4.4	7.9	6.1
Brazil	793	85.6	14.4	7.3	5.5	1.5	0.0	7.1	5.4
Cuba	23	8.7	91.3	65.2	13.0	13.0	0.0	26.1	13.0
Czech Republic	16	87.5	12.5	6.3	0.0	0.0	6.3	6.3	6.3
Dominican Republic	117	47.9	52.1	22.2	11.1	12.8	6.0	29.9	19.7
England & Wales	148	67.6	32.4	12.2	13.5	5.4	1.4	20.3	16.9
Estonia	26	53.8	46.2	7.7	11.5	15.4	11.5	38.5	19.2
France	195	78.5	21.5	12.3	7.2	0.5	1.5	9.2	4.1
India (Delhi state)	*								
Ivory Coast	**								
Kenya	46	63.0	37.0	30.4	6.5	0.0	0.0	6.5	0.0
Latvia	228	26.3	73.7	4.8	18.0	33.8	17.1	68.9	54.4
Lesotho	53	66.0	34.0	20.8	5.7	5.7	1.9	13.2	5.7
Nepal	**								
Netherlands	*								
New Zealand	19	94.7	5.3	5.3	0.0	0.0	0.0	0.0	0.0
Northern Ireland	**								
Peru	458	64.0	36.0	16.2	10.9	6.3	2.6	19.9	15.7
Portugal	117	62.4	37.6	12.0	11.1	9.4	5.1	25.6	18.8
Puerto Rico	22	72.7	27.3	4.5	13.6	4.5	4.5	22.7	13.6
Republic of Korea	189	47.1	52.9	14.3	14.8	16.9	6.9	38.6	27.5
Romania	1,521	63.7	36.3	16.7	10.5	9.1	0.0	19.6	14.4
Russia (Ivanovo Oblast)	33	0.0	100.0	45.5	30.3	18.2	6.1	54.5	27.3
Scotland	**								
Sierra Leone	172	47.1	52.9	16.3	24.4	5.2	7.0	36.6	12.8
Spain (Barcelona)	44	70.5	29.5	9.1	4.5	9.1	6.8	20.5	20.5
Swaziland	44	79.5	20.5	9.1	4.5	2.3	4.5	11.4	9.1
Thailand	**								
United States of America	833	76.4	23.6	12.5	5.9	3.2	2.0	11.2	7.1
Viet Nam	**								
Zimbabwe	36	86.1	13.9	5.6	5.6	2.8	0.0	8.3	8.3
MEDIAN	114.0	64.0	36.0	12.2	9.7	5.4	4.4	19.9	13.0
minimum	16	0.0	5.3	4.5	0.0	0.0	0.0	0.0	0.0
maximum	1,521	94.7	100.0	65.2	30.3	33.8	17.1	68.9	54.4
WEIGHTED MEAN***	465.0	68.2	31.8	14.7	8.9	5.8	2.4	17.1	11.8

* Only combined data reported. **Only primary drug resistance data reported.

*** Arithmetic mean weighted by the estimated number of smear-positive cases of tuberculosis in 1995 for the country or region surveyed.

Acquired resistance to INH ranged from 5.3% (New Zealand) to 70% (Latvia). Resistance to SM among previously treated patients was also common, with a median prevalence of 16% but reaching 82.6% in Cuba. Acquired resistance to EMB was much less common (median 6%). Acquired RMP resistance, on the other hand, was common (median 17%), with prevalence ranging from 0% (Kenya and New Zealand) to 58% (Latvia). The median prevalence of acquired MDR-TB was 13%, with a range of 0% (Kenya) to 54% (Latvia) [Figures 8 and 9]. The average prevalence of acquired resistance to

Fig. 8. Prevalence of acquired drug resistance to any drug and MDR TB, 1994-1997



one (i.e., any monoresistance), two, three or all four drugs is also noted at the bottom of Table 14, and their relative prevalence in the countries studied is illustrated in Figure 10. Resistance to all 4 drugs among previously treated patients was reported in a median of 4.4% of the cases (range 0 to 17%).

Fig. 9. Prevalence of acquired drug resistance in 25 countries and regions, 1994-1997

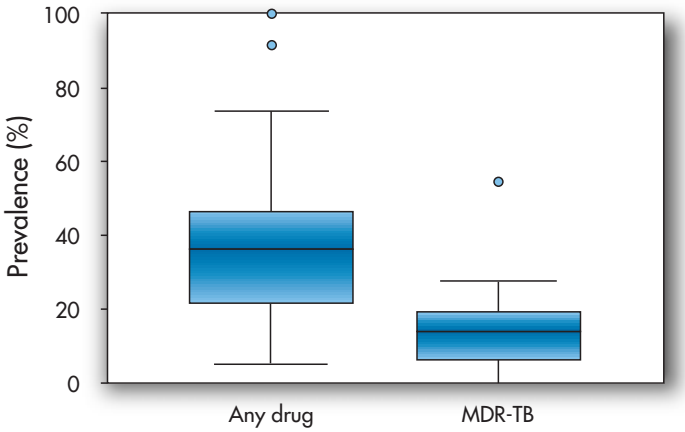
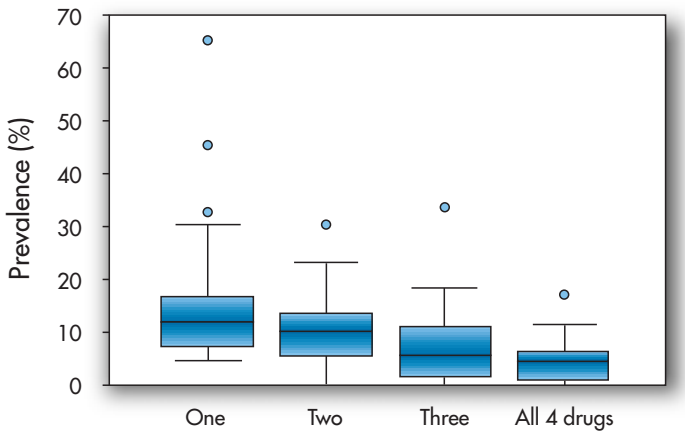
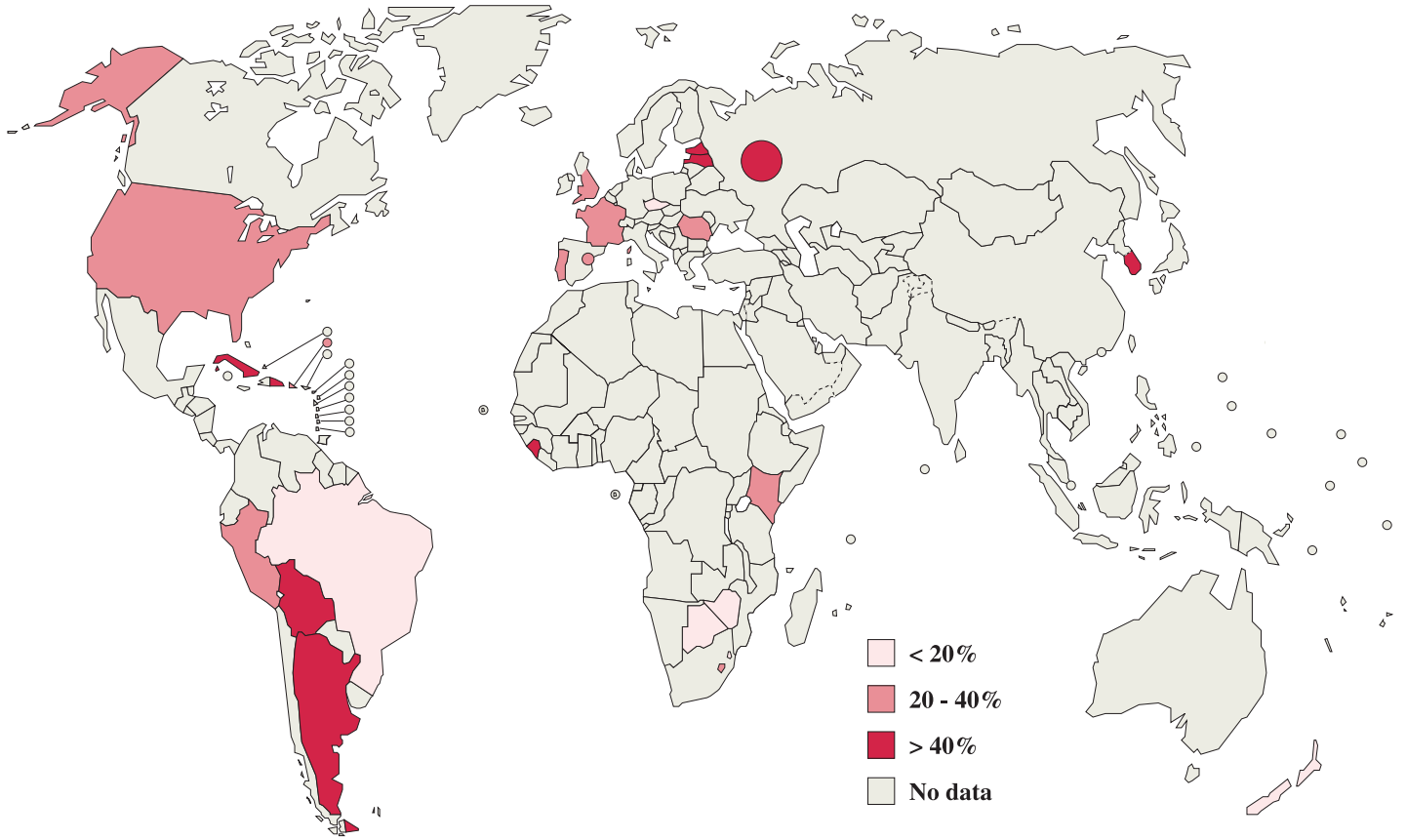


Fig. 10. Prevalence of acquired resistance to 1, 2, 3, or to all 4 first-line anti-tuberculosis drugs



In each boxplot, the horizontal line accross each box represents the median value, and the bottom and top of the box are the 25th and 75th percentiles; the whiskers are 1.5 times the interquartile range, and outliers are noted individually

Map 4a. Prevalence of acquired resistance to any of the 4 anti-tuberculosis drugs in countries and regions surveyed, 1994-1997



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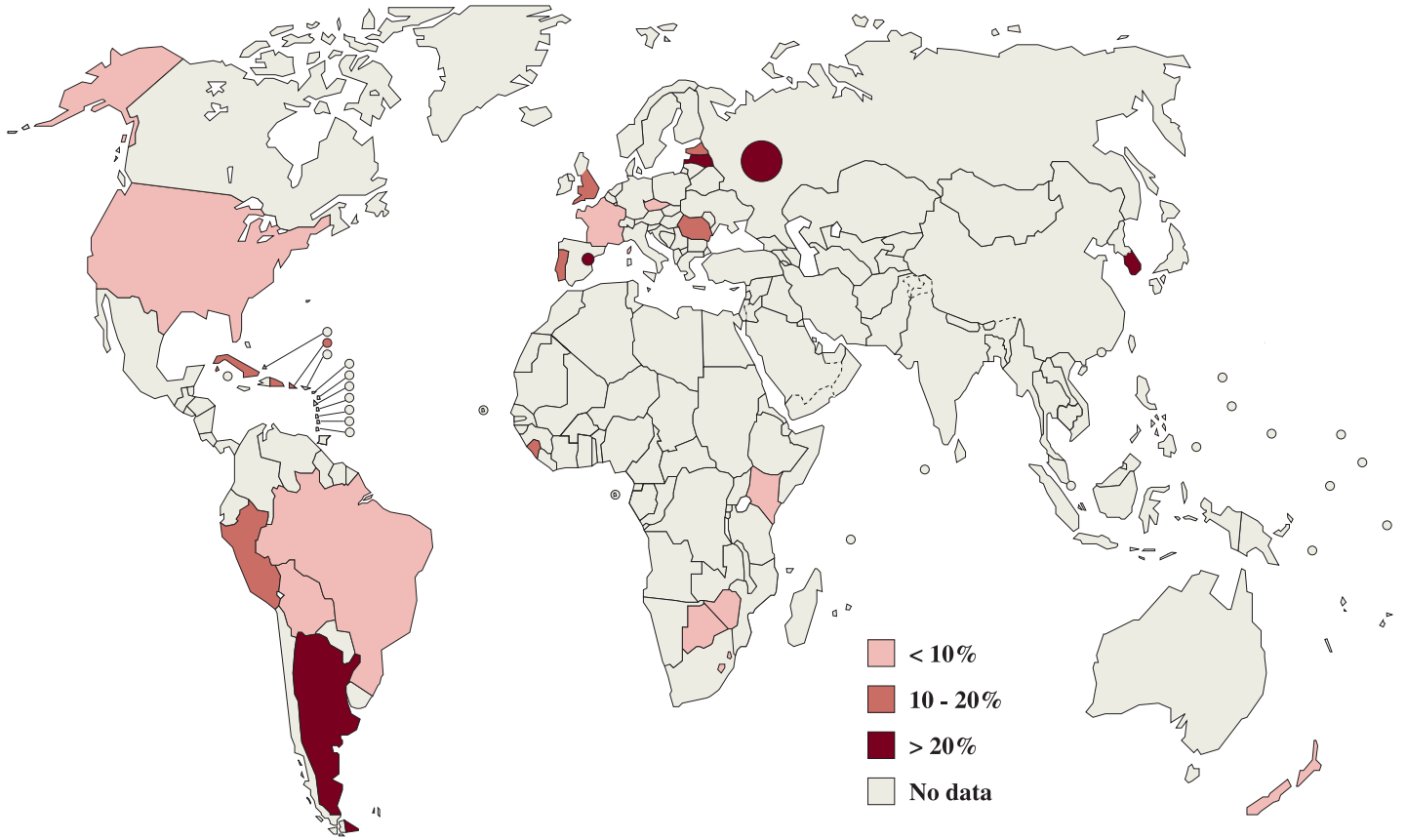
Map 4b. Prevalence of acquired MDR-TB in countries and regions surveyed, 1994-1997



MAP 4b

3.4.3 Combined drug resistance

The overall prevalence of drug resistance, i.e., prevalence of drug resistance regardless of history of prior treatment, was also assessed. In a few countries such as the Netherlands, India and Australia, reliable clinical information was not available to enable a distinction

Table 15. Combined Prevalence of Drug Resistance to each drug by Country, 1994-1997

COUNTRY	*Patients tested*	*INH*		*RMP*		*EMB*		*SM*	
		mono	*any*	*mono*	*any*	*mono*	*any*	*mono*	*any*
Argentina	*	2.8	12.5	0.7	9.2	0.2	5.2	4.0	10.9
Australia	705	1.7	7.5	0.3	1.1	0.0	0.3	1.6	7.5
Benin	**								
Bolivia	*	6.1	10.3	5.1	9.2	3.9	5.6	8.1	11.1
Botswana	*	1.5	2.4	0.8	1.7	0.0	0.5	1.6	2.2
Brazil	*	3.8	6.3	0.2	1.5	0.1	0.2	2.4	3.8
Cuba	786	1.3	2.8	0.1	1.4	0.0	0.0	7.5	9.2
Czech Republic	*	1.2	2.3	0.0	1.2	0.0	1.2	0.0	1.2
Dominican Republic	*	8.8	22.4	7.2	18.6	0.3	5.1	8.9	21.8
England & Wales	2,890	3.6	6.8	0.2	2.1	0.0	0.4	1.1	2.9
Estonia	*	4.7	25.3	0.0	11.7	0.6	9.2	5.3	24.0
France	*	1.2	4.5	0.4	1.3	0.1	0.5	4.6	7.5
India (Delhi state)	2,240	8.1	28.8	0.3	14.0	0.2	7.0	2.4	18.1
Ivory Coast	**								
Kenya	*	10.4	12.4	0.0	0.0	0.0	0.0	0.0	2.0
Latvia	*	4.9	39.0	0.3	23.0	0.0	7.4	1.7	35.1
Lesotho	*	5.9	9.3	0.0	1.2	0.0	0.2	1.1	3.9
Nepal	**								
Netherlands	1,104	4.4	8.6	0.1	1.2	0.0	0.4	5.4	8.7
New Zealand	437	3.2	4.3	0.0	0.7	0.0	0.5	0.5	0.9
Northern Ireland	**								
Peru	*	3.4	10.0	1.8	7.0	0.4	2.3	5.4	10.0
Portugal	*	2.1	9.8	0.0	3.8	0.0	1.0	6.6	13.5
Puerto Rico	391	4.1	7.7	0.5	3.6	1.3	3.6	1.0	2.8
Republic of Korea	*	4.9	10.0	0.4	4.0	0.5	4.2	1.5	3.5
Romania	*	3.9	9.2	0.6	4.3	1.7	1.7	0.0	4.1
Russia (Ivanovo Oblast)	*	3.2	18.7	2.5	12.1	0.8	9.4	13.1	29.7
Scotland	**								
Sierra Leone	*	3.9	21.4	0.3	4.9	0.5	4.1	11.8	28.9
Spain (Barcelona)	*	2.7	5.4	0.4	2.7	1.7	2.3	4.0	5.8
Swaziland	*	3.7	9.6	0.0	1.9	0.3	1.4	2.9	8.3
Thailand	**								
United States of America	14,344	4.2	8.4	0.6	2.7	0.6	2.1	3.1	6.4
Viet Nam	**								
Zimbabwe	*	1.6	4.0	0.0	2.4	0.0	0.5	0.0	0.9
MEDIAN	n/a	3.7	9.2	0.3	2.7	0.2	1.5	2.7	7.5
minimum	n/a	1.2	2.3	0.0	0.0	0.0	0.0	0.0	0.9
maximum	n/a	10.4	39.0	7.2	23.0	3.9	9.4	13.1	35.1
WEIGHTED MEAN***	n/a	5.0	12.2	0.8	5.5	0.5	2.7	2.9	8.1

* Combined drug resistance prevalence was calculated from primary and acquired figures (Australia, India and The Netherlands provided combined data directly); except for countries with surveillance of virtually 100% of TB patients, acquired drug resistance prevalence was weighted by the proportion of cases for retreatment in the NTP. ** Only primary drug resistance reported (combined prevalence not computed). *** Arithmetic mean weighted by the estimated number of smear-positive cases of tuberculosis in 1995 for the country or region surveyed.

between primary and acquired drug resistance to be made. Other countries performed routine surveillance with sampling of virtually all cases presenting for treatment. In both of these situations the reported data were used directly to estimate the prevalence of combined drug

Table 16. Combined Prevalence of Drug Resistance by Country, 1994-1997

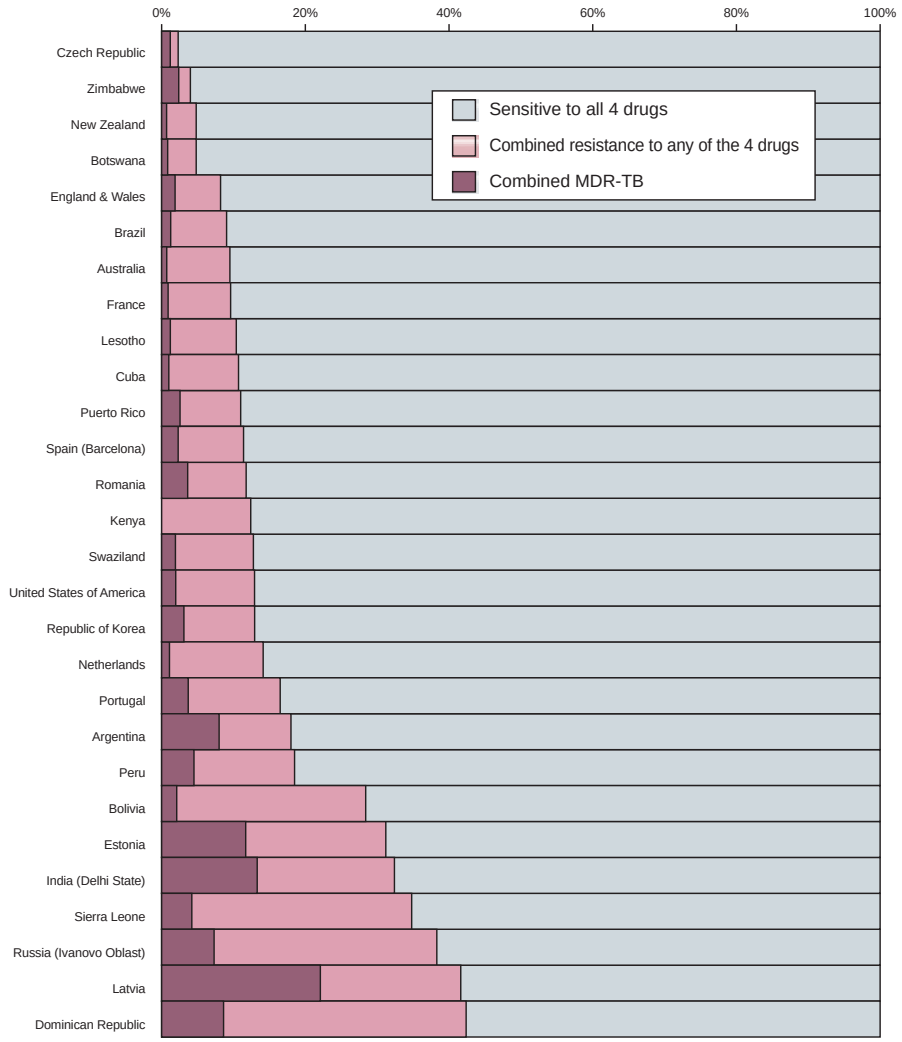
COUNTRY	Patients tested	OVERALL		RESISTANCE TO:				POLY-RESISTANCE	
		Suscept.	Resist.	1 Drug	2 Drugs	3 Drugs	4 Drugs	any	MDR
Argentina	*	82.0	18.0	7.7	3.9	3.6	2.9	10.4	8.0
Australia	705	90.5	9.5	3.5	5.1	0.7	0.1	6.0	0.7
Benin	**								
Bolivia	*	71.6	28.4	23.2	5.8	0.2	0.2	6.2	2.1
Botswana	*	95.2	4.8	3.8	0.5	0.1	0.4	1.0	0.8
Brazil	*	91.0	9.0	6.5	2.4	0.2	0.0	2.5	1.3
Cuba	786	89.3	10.7	8.9	0.9	0.9	0.0	1.8	1.0
Czech Republic	*	97.7	2.3	1.2	0.0	0.0	1.2	1.2	1.2
Dominican Republic	*	57.6	42.4	25.2	10.9	4.2	2.0	17.2	8.6
England & Wales	2,890	91.8	8.2	5.0	2.5	0.6	0.1	3.2	1.9
Estonia	*	68.8	31.2	10.7	7.9	7.0	5.7	20.5	11.7
France	*	90.4	9.6	6.3	2.6	0.5	0.2	3.3	0.9
India (Delhi state)	2,240	67.6	32.4	10.9	10.9	7.1	3.5	21.5	13.3
Ivory Coast	**								
Kenya	*	87.6	12.4	10.4	2.0	0.0	0.0	2.0	0.0
Latvia	*	58.4	41.6	7.0	13.5	14.2	7.0	34.7	22.1
Lesotho	*	89.6	10.4	7.0	2.6	0.6	0.1	3.4	1.2
Nepal	**								
Netherlands	1,104	85.9	14.1	10.0	3.7	0.4	0.1	4.2	1.1
New Zealand	437	95.2	4.8	3.7	0.7	0.5	0.0	1.1	0.7
Northern Ireland	**								
Peru	*	81.5	18.5	11.0	4.9	1.8	0.7	7.5	4.5
Portugal	*	83.5	16.5	8.8	4.8	2.2	0.8	7.8	3.7
Puerto Rico	391	89.0	11.0	6.9	2.0	1.5	0.5	4.1	2.6
Republic of Korea	*	87.1	12.9	7.3	3.0	2.0	0.6	5.6	3.1
Romania	*	88.2	11.8	6.2	3.2	2.3	0.0	5.5	3.6
Russia (Ivanovo Oblast)	*	61.7	38.3	19.5	9.8	5.0	4.0	18.7	7.3
Scotland	**								
Sierra Leone	*	65.2	34.8	16.5	14.0	2.2	2.0	18.2	4.2
Spain (Barcelona)	*	88.6	11.4	8.7	1.2	0.8	0.6	2.7	2.3
Swaziland	*	87.2	12.8	6.9	4.0	1.3	0.6	5.9	1.9
Thailand	**								
United States of America	14,344	87.1	12.9	8.4	3.0	0.8	0.7	4.5	2.0
Viet Nam	**								
Zimbabwe	*	96.0	4.0	1.6	1.5	0.3	0.5	2.4	2.4
MEDIAN	n/a	87.4	12.6	7.5	3.1	0.9	0.6	5.0	2.2
minimum	n/a	57.6	2.3	1.2	0.0	0.0	0.0	1.0	0.0
maximum	n/a	97.7	42.4	25.2	14.0	14.2	7.0	34.7	22.1
WEIGHTED MEAN***	n/a	83.3	16.7	9.1	4.6	2.1	1.0	7.7	4.3

* Combined drug resistance prevalence was calculated from primary and acquired figures; excep for countries with surveillance of virtually 100% of TB patients, acquired drug resistance prevalence was weighted by the proportion of cases for retreatment.

** Only new patients reported (combined prevalence not computed) *** Arithmetic mean weighted by the estimated number of smear-positive cases of tuberculosis in 1995 for the country or region surveyed.

resistance. In the remaining countries, a weighted estimate was calculated based on observed primary and acquired drug resistance, and the reported proportion of retreatment cases in the country or region among smear positive patients registered for treatment.

Fig. 11. Prevalence of combined drug resistance to any drug and MDR TB, 1994-1997

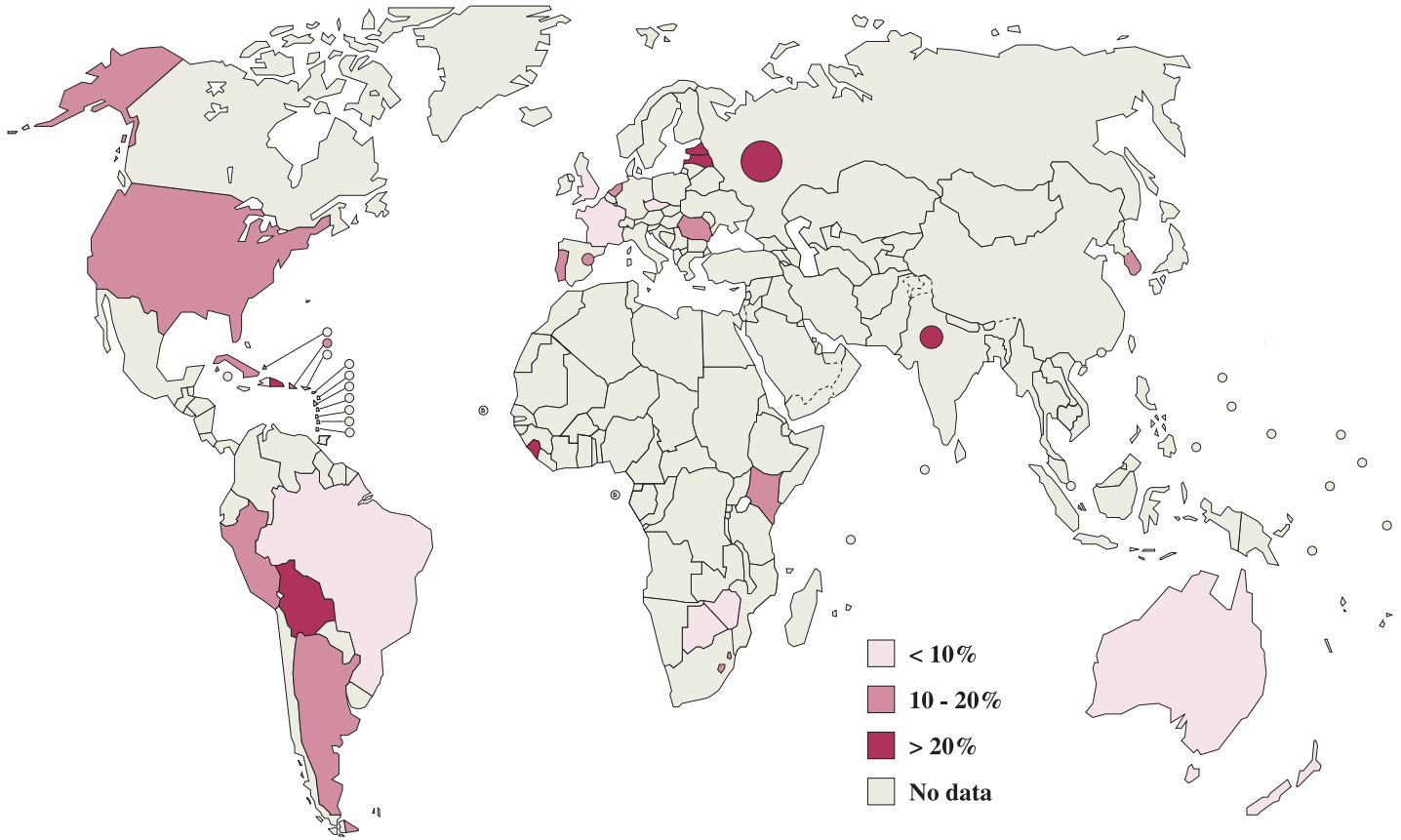


Since the proportion of previously treated patients in most countries was approximately 9%, the combined prevalence of drug resistance resembled the prevalence of primary drug resistance (Tables 15 and 16). The combined prevalence of resistance to any drug ranged from 2.3% (Czech Republic) to 42% (Dominican Republic and Latvia), with a median value of 13%. Resistance to INH ranged from 2.3% (Czech Republic) to 39% (Latvia) and had a median value of 9%. Overall resistance to SM was also common (median value of 7.5%), while combined prevalence of resistance to RMP (2.7%) and EMB (1.5%) was low.

The average proportion of TB patients in surveyed areas with resistance to one (i.e., any monoresistance), two, three or all four drugs is also noted at the bottom of Table 16. Combined resistance to all 4 drugs was found in a median of 0.6% of cases (range 0 to 7%). The median prevalence of MDR-TB overall was 2.4%, with a range between 0% (Kenya) and 22% (Latvia) [Figure 11].

Maps 5a and 5b respectively depict the combined prevalence of resistance to any drug and MDR-TB in the countries surveyed. Drug resistance prevalence is quite high in Eastern Europe, particularly in Latvia. In the Americas, the Dominican Republic and Argentina stand out with high levels of drug resistance. In the few African countries surveyed, the prevalence of drug resistance was low, except in Cote d'Ivoire. The figures for MDR-TB in the Baltic countries are very high, and the situation is serious in Russia too (although at present resistance to SM seems the main problem). Finally, the reports emerging from Asia also document a high prevalence of drug resistance.

Map 5a. Combined prevalence of resistance to any of the 4 anti-tuberculosis drugs, 1994-1997



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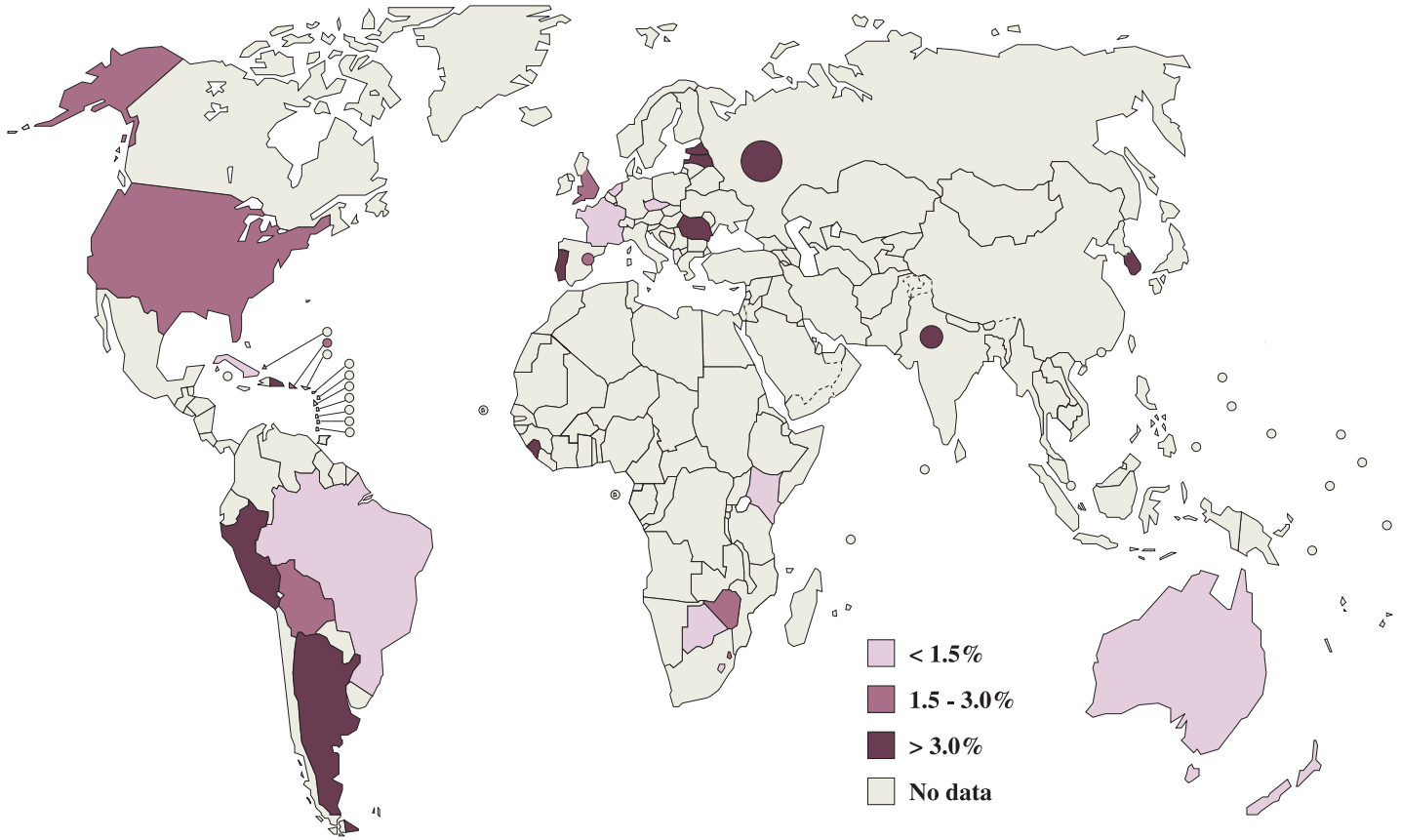
Map 5b. Combined prevalence of MDR-TB, 1994-1997



MAP 5b

3.4.4 Additional indices of drug resistance

While not the primary focus of this document, additional parameters were obtained. Table 17 lists the figures for each country and summary values for selected indeces.

Table 17. Additional indices of drug resistance*

COUNTRY	Primary MDR (%)	Index of MDR Risk (%)	Acquired MDR (%)	Retreat-ment cases (%)	Acquired MDR index (%)
Argentina	4.6	3.6	22.2	19.1	4.2
Australia	(0.7)	(7.2)		9.4	
Benin	0.3	5.1		9.6	
Bolivia	1.2	13.9	4.7	24.8	1.2
Botswana	0.2	2.0	6.1	10.0	0.6
Brazil	0.9	5.2	5.4	7.7	0.4
Cuba	0.7	1.6	13.0	6.9	0.4
Czech Republic	1.0	1.0	6.3	2.9	0.2
Dominican Republic	6.6	22.8	19.7	15.5	3.0
England & Wales	1.1	4.7	16.9	9.2	0.9
Estonia	10.2	10.9	19.2	16.9	3.2
France	0.5	3.1	4.1	10.0	0.4
India (Delhi state)	(13.3)	(16.3)		26.8	
Ivory Coast	5.3	5.9		6.0	
Kenya	0.0	6.3	0.0	20.0	0.0
Latvia	14.4	17.6	54.4	19.2	10.5
Lesotho	0.9	7.0	5.7	6.4	0.4
Nepal	1.1	5.0		7.7	
Netherlands	(1.1)	(7.6)		7.0	
New Zealand	0.7	3.6	0.0	3.4	0.0
Northern Ireland	1.7	0.0		9.0	
Peru	2.5	7.2	15.7	15.0	2.4
Portugal	1.7	5.5	18.8	11.7	2.2
Puerto Rico	1.9	5.7	13.6	6.0	0.8
Republic of Korea	1.6	6.8	27.5	6.0	1.7
Romania	2.8	5.3	14.4	7.4	1.1
Russia (Ivanovo Oblast)	4.0	10.1	27.3	14.0	3.8
Scotland	0.3	2.4		4.0	
Sierra Leone	1.1	12.5	12.8	26.9	3.4
Spain (Barcelona)	0.5	3.2	20.5	9.0	1.8
Swaziland	0.9	8.1	9.1	12.5	1.1
Thailand	3.8	20.6		2.8	
United States of America	1.6	6.8	7.1	7.1	0.4
Viet Nam	2.3	18.9		11.4	
Zimbabwe	1.9	1.3	8.3	7.1	0.6
MEDIAN	1.4	5.9	13.0	9.0	1.1
minimum	0.0	0.0	0.0	3.0	0.0
maximum	14.4	22.8	54.4	27.0	10.5
WEIGHTED MEAN**	2.1	10.8	11.8	10.0	1.2

* See definitions and explanations in section 3.4.4. Spaces were left in blank when either primary or acquired drug resistance was not reported separately; combined prevalence estimates are noted in parenthesis.

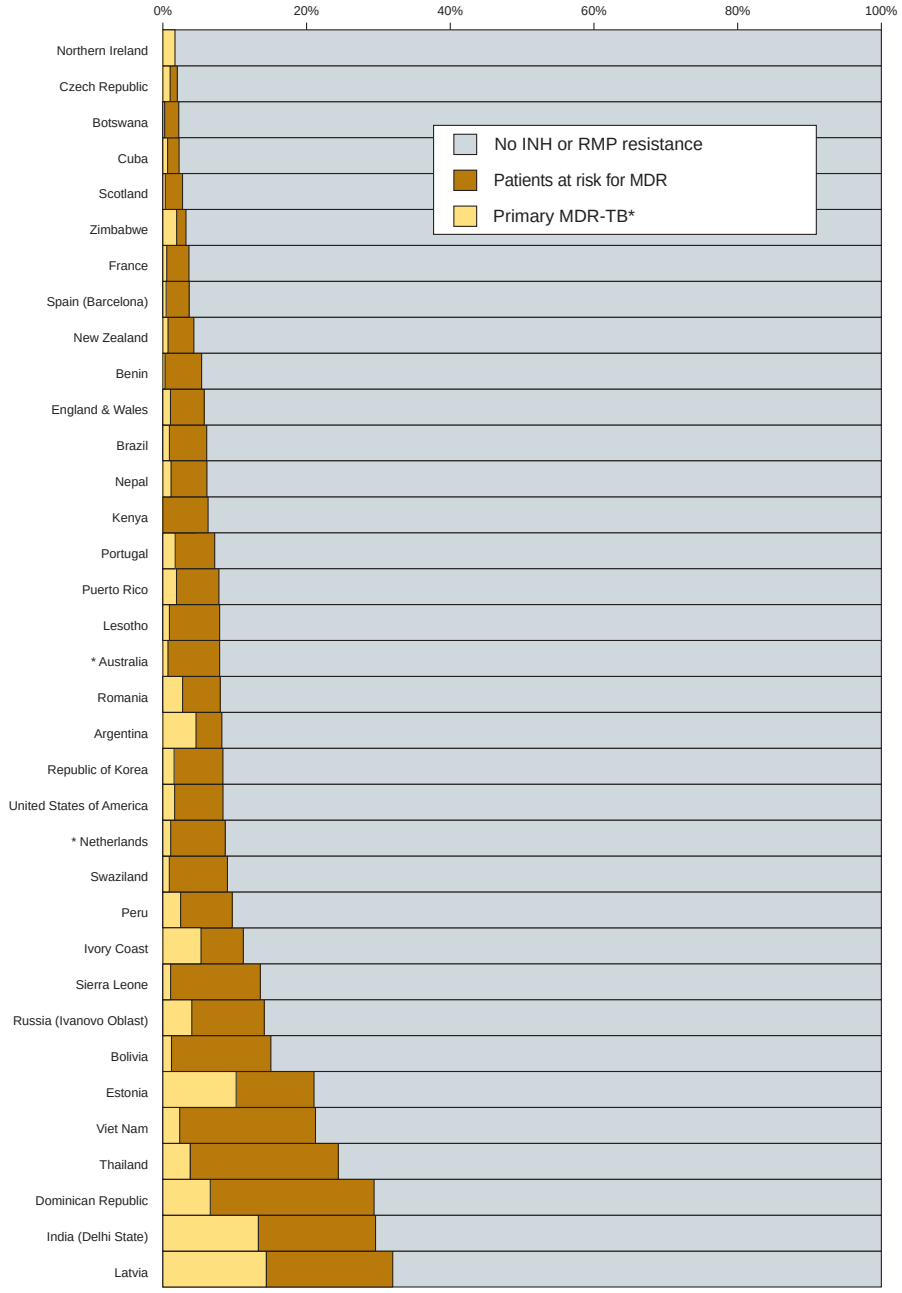
** Arithmetic mean weighted by the estimated number of smear-positive cases of tuberculosis in 1995 for the country or region surveyed.

A relative indicator of how much opportunity there is in a population for additional MDR-TB to develop beyond the MDR already present is given by the sum of the prevalence of resistance to INH and RMP other than as components of the already prevalent MDR-TB. This Index of MDR Risk, beyond the current level of MDR, varied from 0 (Northern Ireland) to 23% (Dominican Republic and Kenya). Those fractions of the respective patient population are at high risk of developing MDR-TB in the near future. The median figure for all countries and regions surveyed was 6% (Figure 12).

Finally, we introduce the Acquired MDR Index. Retreatment cases will usually have higher levels of drug resistance than new patients, and the levels are very high regardless of the NTP performance. The drawback of the prevalence of acquired drug resistance is that it ignores the actual proportion of retreatment cases in a given programme, which could itself be more informative than the prevalence of drug resistance among the few or many retreatment cases. Thus, an index that combines both the level of MDR-TB among retreatment cases and the proportion of cases previously treated is desirable[62]. The Acquired MDR Index is calculated by dividing the number of patients with acquired MDR-TB by the total number of smear positive patients presenting for treatment regardless of history of previous therapy (Table 17).

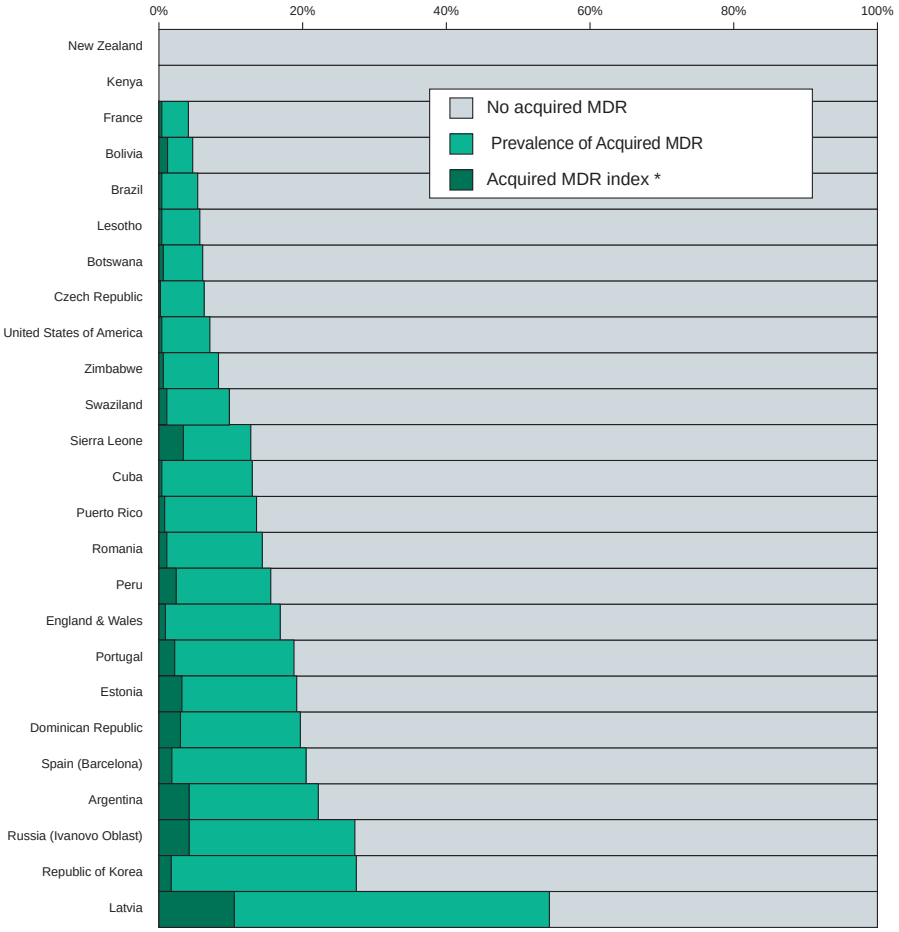
Only 25 countries (none from South-East Asia) provided the required information to calculate the Acquired MDR Index. This parameter correlates well with the proportion of cases presenting for retreatment (r_s = 0.55, p-value <0.01), and with the prevalence of primary drug resistance (r_s = 0.83, p-value <0.01). The values for this parameter ranged from 0 in Kenya and New Zealand, to 10% in Latvia, with a median of 1.1% (Table 17). Figure 13 and Map 6 illustrate the ranking of countries and regions in the Global Project according to the prevalence of acquired MDR and the Acquired MDR Index.

Fig. 12. Primary MDR prevalence plus additional proportion of patients at immediate risk



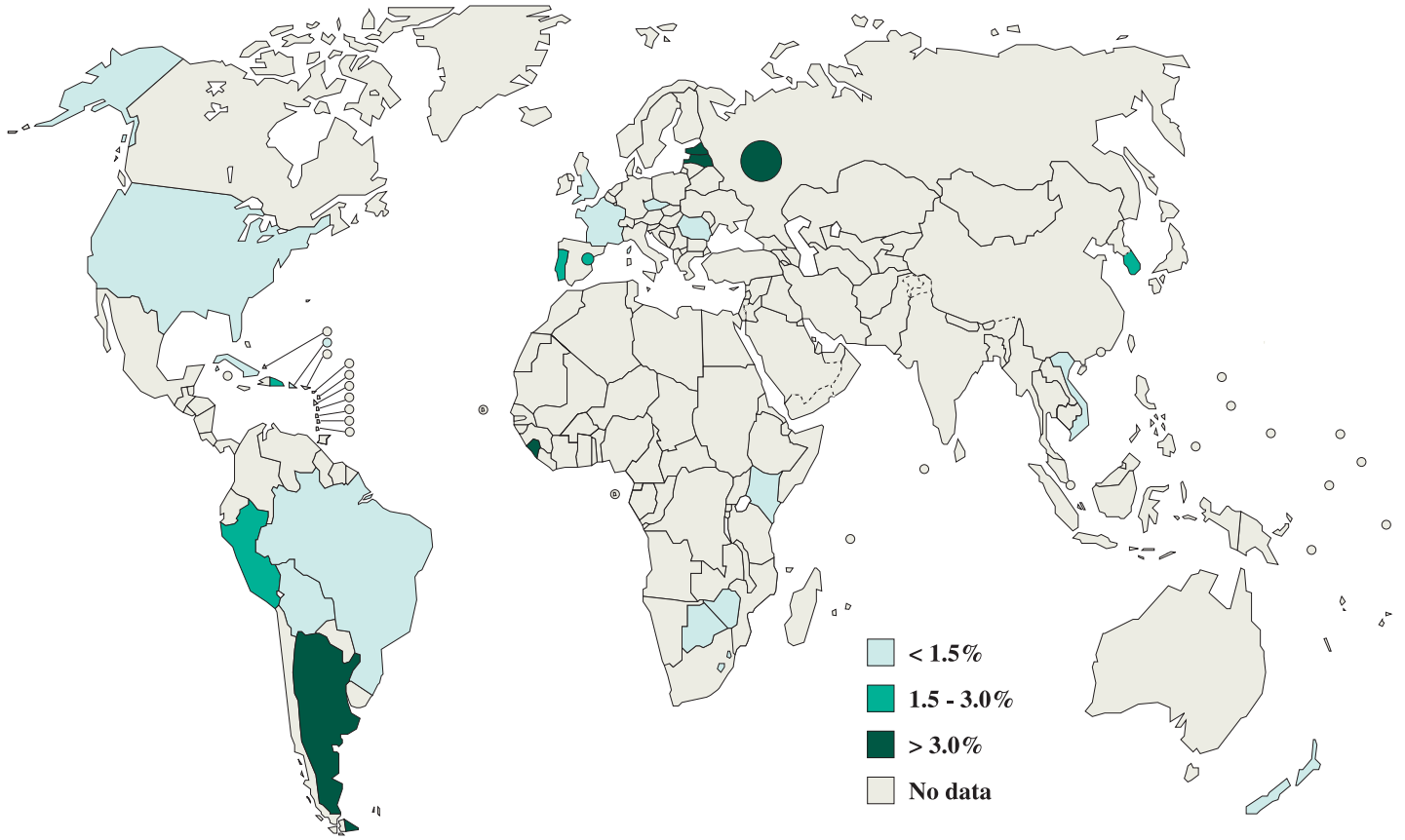
*The figures for Australia, India and The Netherlands are combined estimates of the prevalence of primary and acquired drug resistance.

Fig. 13. Acquired MDR Index by country, 1994-1997



$$\text{* Acquired MDR Index} = \frac{\text{number of patients with acquired MDR-TB}}{\text{total number of patients registered for treatment}}$$

Map 6 Acquired MDR Index for countries and regions in the Global Project, 1994-1997



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3.5 CORRELATION OF DRUG RESISTANCE PREVALENCE WITH ECOLOGICAL CHARACTERISTICS OF THE COUNTRIES SURVEYED

3.5.1 Prevalence of drug resistance across WHO regions and TB control category

Table 18 show the prevalence of anti-tuberculosis drug resistance in each of the five WHO regions for which results were available. Primary MDR-TB was highest in South-East Asia (median 2.5%), and lowest in Sub-Saharan Africa (0.9%). The Index of MDR risk was also highest in South-East Asia (8.4%), illustrating the potential for additional MDR to

Table 18. Prevalence of drug resistance by WHO Region

		Africa	*The Americas*	*Europe*	*South-East Asia*	*Western Pacific*
		n=8	*n=8*	*n=11*	*n=3*	*n=5*
Primary resistance to any drug	Median	8.6	12.4	9.6	23.2	10.4
	Minimum	3.3	8.3	2.0	9.8	4.8
	Maximum	28.1	40.6	34.0	36.6	32.5
Primary MDR	Median	0.9	1.8	1.7	2.5	1.6
	Minimum	0.0	0.7	0.3	1.1	0.7
	Maximum	5.3	6.6	14.4	3.8	2.3
Primary resistance to all 4 drugs	Median	0.0	0.3	0.2	0.7	0.2
	Minimum	0.0	0.0	0.0	0.6	0.0
	Maximum	0.6	1.7	4.6	0.8	0.9
Acquired resistance to any drug	Median	27.2	38.7	36.3		29.1
	Minimum	13.9	14.4	12.5		5.3
	Maximum	52.9	91.3	100.0		52.9
Aquired MDR prevalence	Median	7.2	13.3	18.8		13.8
	Minimum	0.0	4.7	4.1		0.0
	Maximum	12.8	22.2	54.4		27.5
Acquired resistance to all 4 drugs	Median	3.1	2.3	6.1		3.4
	Minimum	0.0	0.0	0.0		0.0
	Maximum	7.0	8.3	17.1		6.9
Combined resistance to any drug	Median	11.4	15.5	13.9	.	9.5
	Minimum	4.0	9.0	2.3	32.4	4.8
	Maximum	34.8	42.4	41.6	32.4	12.9
Combined MDR	Median	1.6	2.3	3.7	.	0.7
	Minimum	0.0	1.0	0.9	13.3	0.7
	Maximum	4.2	8.6	22.1	13.3	3.1
Combined resistance to all 4 drugs	Median	0.5	0.6	1.0	.	0.1
	Minimum	0.0	0.0	0.0	3.5	0.0
	Maximum	2.0	2.9	7.0	3.5	0.6
Index of MDR Risk	Median	6.1	4.6	2.6	8.4	4.0
	Minimum	1.3	1.2	0.0	2.0	2.0
	Maximum	12.5	15.5	5.5	11.5	7.8
Acquired MDR Index	Median	0.6	1.0	2.2		0.0
	Minimum	0.0	0.4	0.2		0.0
	Maximum	3.4	4.2	10.5		1.7

* Acquired drug resistance was not reported separately in any of the countries and regions surveyed in South-Est Asia.

develop. The Acquired MDR Index was highest in Europe (median 2.2%), especially in the former USSR countries, and it was low in the other WHO regions surveyed (approximately 0.6%; no data for South-East Asia).

Table 19. Prevalence of anti-tuberculosis drug resistance by WHO control category

	WHO TB control categorization [d]		
	Good TB control	*Poor TB control*	*Total*
	n = 21	*n = 14*	*n=35*
Any primary drug resistance	9.4	10.7	9.9
Primary MDR *	1.4	1.9	1.4
Primary resistance to all 4 drugs *	0.2	0.5	0.2
Any acquired drug resistance	35.0	36.3	36.0
Aquired MDR *	7.7	19.2	13.0
Acquired resistance to all 4 drugs	2.3	6.0	4.4
Any drug resistance, combined *	11.7	15.4	12.6
Combined MDR **	1.6	5.5	2.2
Combined resistance to all 4 drugs **	0.5	1.3	0.6
Index of MDR Risk	6.1	5.3	5.9
Acquired MDR Index *	0.6	1.8	1.0

[d] Definitions: Good TB control - Countries in WHO Categories 4 and 5 and those in Category 3 with >33% WHO-DOTS coverage. Poor TB control - Countries in WHO Categories 1 and 2 and those in Category 3 with <33% WHO-DOTS coverage (the median figure for the group). * p-value < 0.05 ** p-value < 0.01 (two-tailed t test)

The prevalence of drug resistance across levels of implementation of the WHO TB control strategy is shown in Figure 14. Countries in which over 90% of the population has access to the WHO DOTS strategy have, as a group, lower levels of drug resistance. After categorising countries as having good or poor TB control status, the differences are statistically significant (Table 19). A strong association was noted between TB control category and the Acquired MDR Index: countries with good TB status had a median of 0.6% for this parameter compared with 1.8% in countries with poor TB control (Figure 15).

In Table 20 we have grouped countries according to the prevailing level of primary MDR-TB. Most countries surveyed in Africa had a prevalence of MDR-TB under 1%, while half of the countries surveyed in South-East Asia had MDR-TB levels above 2% in their patient population. Half the countries or regions in WHO Category 1 had primary MDR-TB levels above 2%, compared with 20% for those in Categories 3 and 4, and none of the four countries in Category 5 (Table 20). The lower part of Table 20 again illustrates the association between TB control status and the prevalence of MDR: 50% of countries or regions with poor TB control had an MDR prevalence above 2%, compared with only 17% of the countries with good TB control status.

Table 21 shows Spearman rank (r_s) correlations between the prevalence of drug resistance and several factors at country level. First, there was no correlation between TB notification rates and prevalence of drug resistance. There was no significant association between the reported rates of treatment success (i.e., cure plus treatment completion) and the levels of drug resistance at country or regional level. Finally, the proportion of retreatment cases directly correlated with the prevalence of drug resistance (see also Fig. 16).

Fig. 14. Median prevalence of anti-tuberculosis drug resistance by category of TB control, 1994-1997

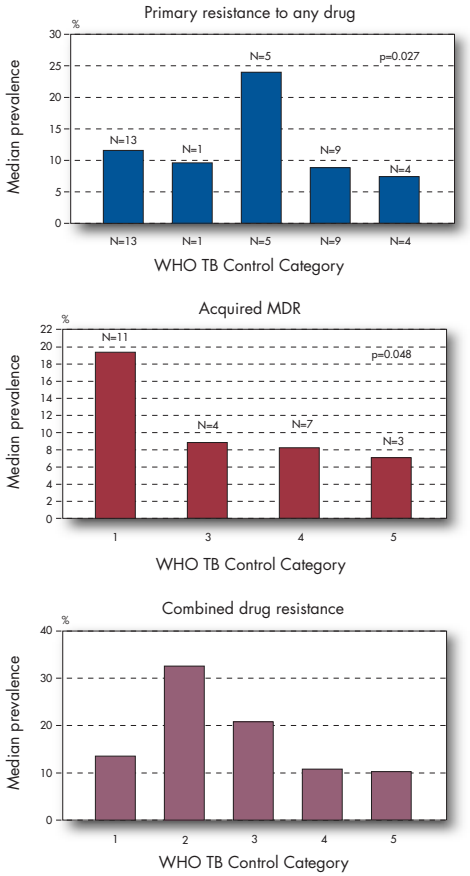
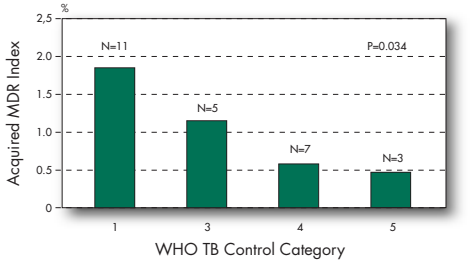
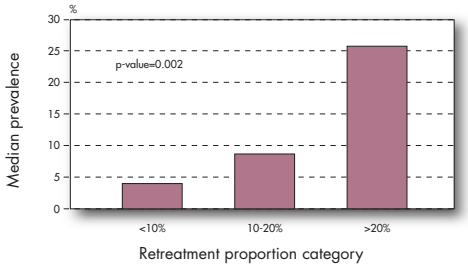


Fig. 15. Acquired MDR Index by WHO control category, 1994-1997

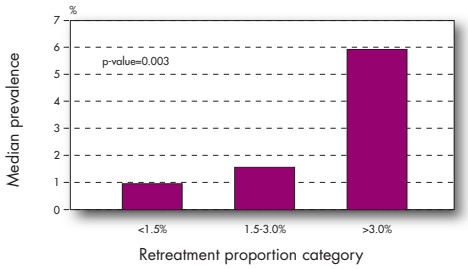


WHO TB control categories:
1. Not accepting WHO TB control strategy and TB notification rate > 10/100,000
2. Implementing WHO TB control strategy in less than 10% of the population
3. Implementing WHO TB control strategy in 10 to 90% of the population
4. Implementing WHO TB control strategy in over 90% of the population
5. Not accepting WHO TB control strategy and TB notification rate < 10/100,000

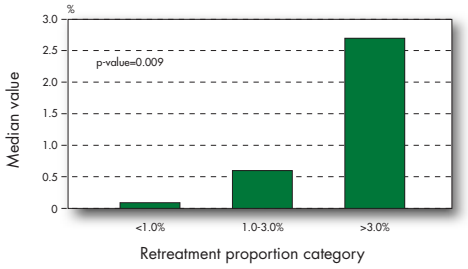
Fig. 16. Association between proportion of retreatment cases and drug resistance



A. Primary resistance to any drug by the proportion of cases for retreatment



B. Combined MDR-TB levels by the proportion of cases for retreatment



C. Acquired MDR-TB Index by the proportion of cases for retreatment

Table 20. Level of primary MDR by WHO region and TB control status

		PRIMARY MDR-TB PREVALENCE		
		< 1.0%	1.0 - 2.0%	> 2.0%
	N*	11	11	10
WHO Region				
Africa	8	62.5%	25.0%	12.5%
The Americas	8	25.0%	37.5%	37.5%
Europe	11	27.3%	36.4%	36.4%
Southeast Asia	2	0.0%	50.0%	50.0%
Western Pacific	3	33.3%	33.3%	33.3%
WHO Surveillance/DOTS category				
1. Not accepting WHO TB control strategy and TB notification rate > 10/100,000	13	38.5%	7.7%	53.8%
2. Implementing WHO TB control strategy in less than 10% of the population	1		100.0%	
3. Implementing WHO TB control strategy in 10 to 90% of the population	5	20.0%	60.0%	20.0%
4. Implementing WHO TB control strategy in over 90% of the population	9	44.4%	33.3%	22.2%
5. Not accepting WHO TB control strategy and TB notification rate < 10/100,000	4	25.0%	75.0%	
Proportion of TB patients presenting for retreatment**				
<5%	5	50.0%	25.0%	25.0%
5-10%	14	43.8%	43.8%	12.5%
>10%	13	16.7%	25.0%	58.3%
Dichotomous TB control status/*****				
Good TB control	18	33.3%	50.0%	16.7%
Poor TB control	14	35.7%	14.3%	50.0%
TOTAL	32	34.4%	34.4%	31.3%

*Number of countries or regions surveyed: a total of 32 reported primary drug resistance. ** Chi square p-value < 0.05.
***Definitions: Good TB control - countries in WHO Categories 4 and 5 and those in Category 3 with >33% WHO-DOTS coverage.
Poor TB control - countries in WHO Categories 1 and 2 and those in Category 3 with <33% WHO-DOTS coverage.

3.5.2 Correlation between characteristics of the TB patient population and the prevalence of anti-tuberculosis drug resistance

Mainly for reasons of confidentiality, most countries did not provide WHO with individual patient information. Thus we have performed an ecological analysis correlating the prevalence of anti-tuberculosis drug resistance levels with some aggregate characteristics of patient populations (i.e., HIV seroprevalence) at the country level. Information on the proportion of cases born in different regions or countries was not systematically available for the countries surveyed and was not analysed. A preliminary analysis of the 9 countries which are members of OECD (data not shown) did not reveal an association between prevalence of drug resistance and either the proportion of foreign-born people or the rate of asylum seekers and refugees in 1995.

The seroprevalence of HIV infection among TB patients was inversely correlated with the prevalence of MDR (see Table 21). The Spearman rank correlation (r_s) between HIV seroprevalence in TB patients and acquired MDR level was -0.47 (p-value < 0.05).

Table 21. Spearman rank correlation of anti-tuberculosis drug resistance prevalence and factors at country level#

	Any primary drug resistance	Primary MDR	Any acquired drug resistance	Acquired MDR	Any drug resistance, combined	Combined MDR	Acquired MDR Index
TB notification rate (per 100,000)	0.173	0.042	0.002	-0.033	0.169	0.267	0.13
Estimated HIV prevalence among TB patients (%)	-0.181	-0.339	-0.533(**)	-0.468(*)	-0.381(*)	-0.442(*)	-0.376
Currently reported treatment success rate (i.e., cure and completion)	0.009	-0.242	0.203	0.058	0.131	-0.134	-0.18
Retreatment cases among all TB patients (%)	0.441(*)	0.175	0.509(**)	0.194	0.691(**)	0.487(**)	0.628(**)
Duration of National Control Programme	-0.05	0.02	0.169	0.256	0.153	0.298	0.302
Patients treated with SCC regimens (%)	-0.382(*)	-0.215	-0.316	-0.149	-0.458(*)	-0.390(*)	-0.235
Anti-tuberculosis drugs in FDC preparations (%)	0.089	-0.178	0.087	0.129	0.216	0.092	0.096
Year rifampicin was introduced	0.061	-0.037	0.185	-0.196	0.089	-0.076	-0.089

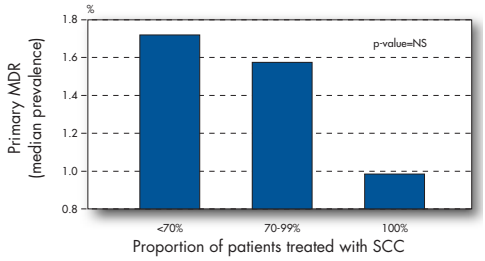
Correlations under 0.40 are poor; those between 0.40 and 0.70 are good; and correlations over 0.70 are excellent
* p-value <0.05 ** p-value <0.01 No adjustments made for multiple comparisons.

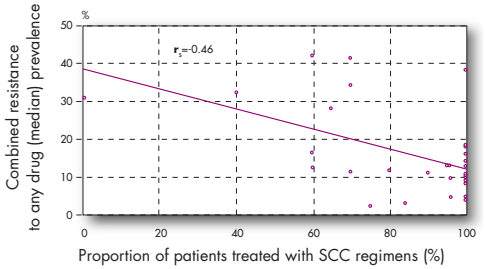
The inverse association (but not the statistical significance) persisted after excluding African countries, where MDR is infrequent and HIV seroprevalence is record high. There was no association between HIV co-infection rate and the prevalence of RMP monoresistance among new TB patients.

3.5.3 Correlation between drug resistance and the different country approaches to anti-tuberculosis treatment

Finally we correlated the level of MDR-TB with prevailing approaches to the treatment of tuberculosis at the country level *at the time of the survey*. We explored the use of standardised SCC, directly observed therapy, FDC preparations, and the proportion of TB patients estimated to be treated in the private sector (Tables 21 and 22). The year in which RMP was introduced in TB routine treatment was also evaluated.

All countries surveyed claimed they recommended standardised anti-tuberculosis treatment regimens. There was, however, variation in the proportion using SCC regimens and DOT. The use of SCC regimens in TB treatment was inversely associated with the prevalence of combined resistance to any drug (r_s=-0.46, p-value < 0.05); countries with MDR levels above 2% reported using SCC in a median 70% of their patients, compared with 100% in countries with MDR levels under 2% (see Fig. 17). On the other hand, there was no association between patterns of directly observed therapy utilisation and the prevalence of drug resistance (Table 22).





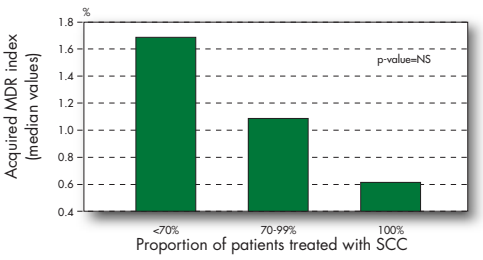


Fig. 17
Correlation between use of short course chemotherapy regimens and levels of anti-tuberculosis drug resistance

The proportion of anti-tuberculosis drugs dispensed in FDC preparations was not significantly correlated with levels of drug resistance (Tables 21 and 22), although it showed a non-significant protective trend when countries were stratified according to the quality of their TB control programme. There was also no significant difference in the prevalence of MDR-TB in countries with no private sector treatment of TB patients and those where over 15% of them were treated outside the public sector (Table 22).

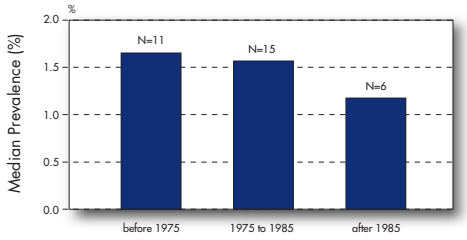
Figure 18 illustrates the importance of the duration of RMP use and the emergence of MDR-TB. While not statistically significant, MDR-TB was relatively rare in countries that introduced RMP in TB treatment after 1985, such as Kenya. This and other associations, however, could be confounded by additional factors in those countries.

Table 22. Level of primary MDR TB by different TB control strategies

			*Primary MDR-TB prevalence **		
		Number of countries**	< 1.0 % n = 11	1.0 - 2.0 % n = 11	> 2.0 % n = 10
Implementation of directly observed therapy					
	Not used	10	20.0%	50.0%	30.0%
	Intensive Rx	12	33.3%	33.3%	33.3%
	Full Rx, <50% pts	5	60.0%	20.0%	20.0%
	Full Rx, >50% pts	5	40.0%	20.0%	40.0%
Patients treated in the private sector					
	Practically none	11	36.4%	27.3%	36.4%
	<15% of patients	11	50.0%	10.0%	40.0%
	>15% of patients	10	20.0%	70.0%	10.0%
Use of fixed-dose combination tablets					
	Less than 33%	16	25.0%	37.5%	37.5%
	Between 33 and 67%	4	50.0%	25.0%	25.0%
	More than 67%	11	45.5%	27.3%	27.3%

*All Chi ^{2} contrasts were nonsignificant at p-value = 0.05. **Australia, India and the Netherlands reported only combined levels of drug resistance and are not included in the categorization according to prevalence of primary MDR-TB.

Fig. 18. Primary MDR-TB prevalence by year of introduction of rifampicin



CHAPTER FOUR

DISCUSSION

4.1 OVERVIEW OF THE PREVALENCE OF DRUG RESISTANCE BY WORLD REGIONS

The results of the Global Project on Anti-tuberculosis Drug Resistance Surveillance provide the first standardised overview of the level of drug resistance in the world. Drug-resistant strains exist in all 35 countries from five continents surveyed. The median prevalence of drug resistance among new tuberculosis patients was 10% with a range from 2% to 40%. While the prevalence of MDR-TB is generally low, there are several countries where the situation warrants prompt intervention. Overall, the median prevalence of primary MDR was 1.4% ranging from 0 to 14%. The prevalence of drug resistance was higher in areas with poor TB control.

In the Americas, the 'hot spot' identified by the Global Project is the Dominican Republic, where the prevalence of any primary drug resistance is 41%, and is 6.6% for MDR-TB. This is probably the result of a deficient NTP, self-medication, irregular drug supply, and the unregulated treatment of tuberculosis patients by private practitioners. HIV infection may be another contributing factor, as may the frequent commuting by Dominicans between the Caribbean and New York City, where MDR was very common in the early 1990s[8]. Demonstration projects introducing the WHO DOTS strategy should be expanded and international cooperation sought to tackle TB before it becomes harder to control. In addition, worrying levels of primary MDR (4.6%) were recorded in Argentina. The rest of the continent, including the United States, enjoys relatively little MDR-TB. This was particularly reassuring in Brazil, which has a high TB burden.

The situation in the African countries surveyed, although heterogeneous as well, is probably best in the world in terms of anti-tuberculosis drug resistance. This has occurred despite the HIV-driven increase in TB[75,76], political unrest and wars in some countries during the last decade. This is probably due not only to the presence of a number of well-organised control programmes, but also to the recent date of introduction of RMP in some

countries and the lack of anti-tuberculosis treatment outside national programmes. However, resistance to INH is present in almost 10% of the cases and RMP is available on the open market; unless control measures are strengthened, MDR-TB will probably emerge in the next decade as has already occurred in the Ivory Coast.

Anti-tuberculosis drug resistance in the world

- Found everywhere to various degrees (median prevalence 10% in new patients).
- MDR-TB has emerged on four continents (median prevalence 1.4% in new patients).
- 'Hot spots' for MDR-TB were identified in the former USSR, Dominican Republic and Argentina, Ivory Coast, and several Asian countries.

In Europe, the prevalence of drug resistance parallels the overall situation with tuberculosis. In Western European countries, where tuberculosis has been declining steadily for decades[77], the median prevalence of primary MDR is below 1%. Even in Barcelona (Spain), where HIV co-infects 28% of TB patients, MDR-TB is infrequent. These figures are well below the average worldwide prevalence and, at least in some countries, the problem seems confined to recent immigrants from areas where TB is poorly controlled[78,79]. Nevertheless, nosocomial outbreaks of MDR-TB among HIV-infected patients, such as those identified by the survey in Italy[80], are a serious concern. Such episodes are reminiscent of the early reports from New York City that were followed by high rates of drug resistance in the general population[81,82].

Over the last decade, on the other hand, Eastern Europe has witnessed a reversal of the century-old decline in tuberculosis incidence[83]. The chaos caused by the fall of the socialist public health system has been accompanied by increases in the death toll of tuberculosis in Russia and other countries of the former USSR. Irregular drug supply, lack of standardised multidrug regimens, and possible nosocomial and prison outbreaks may be contributing factors. The prevalence of primary MDR-TB in the Baltic states is among the highest in the world. Romania reported a mid-range prevalence of MDR-TB, but the sensitivity of DST was low and the true rates could be higher. Russia itself leads Europe with a tuberculosis mortality rate of 15.4 per 100,000. While the prevalence of MDR-TB is not as high as in the Baltics, in the Ivanovo Oblast - 300 km east of Moscow - total primary drug resistance prevalence is already close to 30%. Unless NTPs are rapidly revitalised and sound control policies implemented, MDR-TB is likely to become a serious problem in the region.

Asia remains the stronghold of tuberculosis in the world and a battleground for its control[76,84,85]. Case numbers and rates of tuberculosis increased in some Asian countries between 1984-86 and 1993-95[76]. Korea's survey found little primary drug resistance, consistent with the decline shown by previous periodic surveys in that country[86]. Although directly observed therapy is not used, Korea has a solid control programme with standardised SCC regimens. MDR-TB was also infrequent in Nepal. The situation, however, is different in neighbouring countries. While a final verdict awaits the completion of several ongoing surveys, our preliminary results suggest the problem of drug resistance in the region is quite serious. India alone carries almost a third of the worldwide burden of

tuberculosis[76] and the combined prevalence of MDR-TB in Delhi (13.3%) is similar to that of the Baltics. Similarly, the results of the ongoing surveys in Vietnam and Thailand further document the emergence of MDR-TB in the region.

4.2 STRENGTHS AND LIMITATIONS OF THE GLOBAL PROJECT ON ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

The result of this coordinated international effort is not a complete atlas of the global prevalence of drug resistance. Nonetheless it provides the best and most comprehensive data to date on the prevalence of drug resistance in different countries around the globe. In addition, it has highlighted the strengths and weaknesses of the methods used, and the experience gained of conducting surveys in different regions of the world has been distilled into a revised set of Guidelines for the implementation of future surveys and surveillance programmes on drug resistance prevalence[46].

4.2.1 Strengths of the Global Project

The establishment of a dynamic, expanding multinational system for global drug resistance surveillance is in itself a major achievement. The Global Project is evidence of the concern, will and cooperation of a large number of authorities, investigators and health providers fighting tuberculosis throughout the world.

Laboratory standardisation and the quality assurance programme implemented through the network of SRLs provided the backbone for obtaining reliable and comparable DST results. The network of SRLs is a unique tool providing a vehicle for self-assessment and improvement. This global system is the first in microbiology and could be a model for research and surveillance of other diseases. While the quality of DST was suboptimal in some NRLs, specificity (i.e., ability to detect true drug susceptibility correctly) was excellent overall (i.e., overestimates of MDR-TB levels are unlikely). Moreover, there was no correlation between the level of drug resistance and the specificity of DST for RMP (r_s = -0.02, p=0.67).

Strengths of the Global Project

- Standardised epidemiological methods and definitions.
- Proficiency testing of DST results by SRLs.
- Five continents represented.
- Data on 50,000 patients sampled from 20% of the world's population.

A working consensus on definitions and terminology was a key achievement of this project. The WHO/IUATLD Guidelines[46] effectively provided a common framework for following the prevalence of drug resistance in regions disparate in terms of tuberculosis burden, health care infrastructure, DST methodology and staff training. The Global Project helped build epidemiological capacity in representative sampling, standardised data collection and reporting, and other survey methodologies. The resulting experience and trained personnel may be useful in future surveys of additional aspects of tuberculosis and other national health problems.

4.2.2 Limitations of the study

The major weaknesses of earlier reports on anti-tuberculosis drug resistance prevalence, namely non-representative sampling, non-standardised laboratory methodology, and the inability to distinguish between primary and acquired resistance, were largely overcome by the Global Project. However, there were limitations in implementing protocols at the national and regional levels.

Some countries conducted surveys, while others presented results of their ongoing surveillance systems (mostly the industrialised countries). The reported prevalence of drug resistance, however, should not be significantly biased by either approach as long as patient samples are representative and sufficiently large. Of the 33 studies completed, 25 (75%) achieved over 90% of the sample size originally calculated to obtain precise estimates of the prevalence of drug resistance. The other eight did not, but they all enrolled over 200 patients each, with a mean sample size of 960.

Most studies were countrywide, but a few surveys were conducted in selected regions within a country (e.g. Nepal, Russia and India). However, sampling was deemed representative at the regional level. While most countries studied only smear-positive cases, countries conducting ongoing surveillance tested culture-positive, sputum-negative cases as well. But, there is no association between drug resistance and sputum smear positivity(J. Grosset, pers. comm. 1997).

The number of countries with results of surveys or surveillance programmes to date - 35 - is relatively small compared to the 216 countries, areas and territories listed by WHO. However, drug resistance was directly tested in approximately 50,000 patients systematically or randomly drawn from geographical areas with a total population of over 1 billion (20% of the world's population). Countries from all WHO regions, except those in the Eastern Mediterranean area, are included in the report.

More importantly, the Global Project has surveyed countries at all levels of tuberculosis control. Countries with better TB control and laboratory infrastructure were nevertheless more likely to participate than those where the TB situation is poorer, especially in Africa. We included, for example, 12 of 84 (14%) countries with TB notification rates over 10/100,000 and not following the WHO control strategy, and 10 of 38 (26%) with more than 90% of their population covered by WHO DOTS strategy. We calculated that the countries not surveyed in the Global Project are likely to have higher levels of primary MDR than the countries in this report. Thus, although the Global Project surveyed tuberculosis patients sampled from cases occurring in a fifth of the world's population, the prevalence of drug resistance could be worse than our estimates.

Limitations of the Global Project

- Countries with poor TB control were underrepresented.
- NRL performance was suboptimal in some countries.
- Ecological analysis was limited by the small number of countries and imprecision of some estimates.
- Trends in MDR-TB are not yet available.

Distinguishing accurately between primary and acquired resistance was not always possible. In the absence of easily accessible, comprehensive TB registers, this distinction depends on a patient's history of prior anti-tuberculosis treatment, and on the training and motivation of clinicians. For different reasons patients may be unaware of or prefer to conceal such information. Most surveys in the Global Project noted the Guidelines' emphasis on this issue and took the recommended steps to guarantee the correct classification of new and retreatment cases. For different reasons, India, Australia and the Netherlands did not provide results stratified in this manner. More importantly, undetected misclassification of new and retreatment cases may have occurred in some surveys. Such occurrence could have artificially increased the prevalence of primary drug resistance, as resistance is more common in previously treated patients.

The Henan Province of China, 1996: a case study

Tuberculosis is an important public health problem in China. Following a technical review of the TB control programme undertaken by the Ministry of Public Health with assistance from the World Bank and WHO in 1990-91, a new project of TB control was launched. This project, financed through a World Bank loan with the technical assistance of WHO, targeted 12 Provinces with a population of 573 million. The achievements of this DOTS programme have been impressive, with cure rates of over 90%.

Henan, the largest Province of China, was not included among the 12 Provinces where DOTS was implemented. Thus, the control programme was not revised. The number of new TB patients recorded by the NTP was 39,078 in 1994 (rate 42.9 per 100,000), 10,401 of them bacteriologically proven; HIV infection is virtually non-existent. Reports from routine laboratory work in 1990 had shown a prevalence of primary drug resistance to RMP of 6.5%.

Due to the existence of a well-equipped mycobacteriology laboratory, Henan was considered a suitable Province for a drug resistance survey. The Henan laboratory was linked, for quality control, to the SRL in Korea. Sample size requirement was estimated at 1,075. The proportionate cluster sampling method was used to select 30 of the 118 county diagnostic centres in the Province. Training was conducted on protocol implementation. Cultures were performed on LJ medium; the absolute concentration method was used for DST.

After a pilot phase and a visit by SRL and WHO staff and consultant, the survey was initiated in April 1996. Based on strain exchanges with the SRL at the beginning of the survey, the sensitivity for RMP-resistance in the Henan laboratory was nearly 100%, but specificity was only 88%. In November 1996 a new visit by the SRL representative took place and additional recommendations were made.

Results

By April 1997, 1422 patients had been enrolled and 1372 strains tested (1080 of them from patients without history of prior treatment).

The prevalence of primary resistance to any of the 4 drugs tested was 48.6%, and that of primary MDR was 20.3% (total RMP resistance of 26.2%). Primary RMP-resistance prevalence was high (15%) even after adjusting for the poor specificity in RMP DST. Final verification of results by the SRL in Korea is pending.

In addition to weaknesses in tuberculosis management in the region, methodological explanations were sought. The sample was deemed representative. Laboratory contamination was unlikely given a diversity of resistance patterns. An alternative hypothesis was misclassification of previously treated patients. The team in Henan re-interviewed those patients who had denied previous therapy. Of the 1080 patients, 920 were reached and only 486 (52%) were confirmed as new cases. The revised prevalence of primary drug resistance was 36% and that of MDR-TB 11.3%.

Comments

The experience in Henan provides several lessons. ***First****, a quality assurance programme in collaboration with a SRL must precede the initiation of a survey.* ***Second****, patient's report of previous anti-tuberculosis treatment should not be accepted without proper scrutiny. The erroneous inclusion of previously treated patients in calculating the prevalence of primary MDR-TB may double the estimate. Interviewers should be well trained and the history of anti-tuberculosis treatment should be validated as early as possible.* ***Last****, the revised estimates of drug resistance in Henan are worrying, even if preliminary. As the results from Henan are not representative of China as a whole and, particularly, of the areas covered by the revised control programme based on DOTS, further well-conducted drug resistance surveys are needed to better define the drug resistance situation in China.*

The main limitation of the Global Project is that only cross-sectional data at a single period in time can be provided in this first phase. A complete understanding of the epidemiology of drug resistance in tuberculosis requires longitudinal trends.

The ecological analysis of the determinants of MDR-TB was complicated not only by the lack of longitudinal information, but also by the relatively small number of units of analysis (i.e. countries, not individual patients). This was further compounded by imprecision in the measures of drug supply and treatment patterns[70,87], and the fact that some time lag exists between them and the emergence of drug resistance. Finally, this type of analysis may lead to the so called 'ecological fallacy', or the inappropriate application of the conclusions to individual patients[70,88]. Yet for contagious diseases such as tuberculosis, where community control policies are paramount and individual patient information is incomplete, the analysis of grouped data is appropriate[70,89].

4.3 IMPORTANT LABORATORY ISSUES

The network of SRLs of the Global Project is unique and we put it forward as a model of international scientific collaboration in support of an important public health initiative. The SRLs and their respective heads enabled the Global Project to collect valid results in spite of technological discrepancies around the world and have opened a new chapter in DST. Many of the lessons learned have been published in detail elsewhere[47] or are currently being analysed. The benefits this global network has brought to NRLs will extend beyond the Global Project.

These results update the view expressed by Fox in 1977: "there are probably very few, if any, laboratories in the world that can perform reliable sensitivity tests"[90]. Two decades later, just as drug resistance is emerging as a clinical and epidemiological concern, several laboratories in the world are capable of providing accurate and reliable DST results. There is of course room for improvement and a continuous need to monitor the proficiency of NRLs and smaller laboratories performing DST.

4.3.1 The quality assurance programme

The quality assurance implemented during the last three years across a worldwide network of SRLs achieved several things. It permitted the standardisation of some DST procedures. It also allowed us to ascertain the accuracy and reliability of the different laboratories, providing a solid framework for comparing the prevalence of drug resistance in different countries. Most importantly, the quality assurance programme led to improvements in DST methodology. Individual laboratories, prompted by the nondirective feedback of the results of each round of strain exchange, made their own adjustments and improved their performance over time. The remaining discrepancies for EMB and SM should be further investigated. A fourth proficiency testing exercise has been completed in 1997. This quality assurance programme is expected to continue in the future.

All participating SRLs were based in prestigious institutions. Since no single laboratory could claim perfection in DST, the results of the majority were used as a 'gold standard' within the network. It should be noted that the judicial results were in agreement with laboratories using radiometric techniques for DST. Measured against the judicial result, the overall efficiency and reliability of the SRLs were 96% and 97% respectively despite differences in DST procedures. These figures surpass the 95% mark traditionally used as a 'rule of thumb' in mycobacteriological testing.

One additional merit of the quality assurance programme was the confidential and nondirective nature of the feedback provided to individual laboratories. Questionnaires were sent to laboratories to find out the reasons for any remaining problems. Assistance was offered to those which had difficulties. Changes were introduced to get closer to the specifications of laboratory protocols.

As a result of the quality assurance programme, internationally comparable results of DST could be obtained. We are confident that such results are reliable for INH and RMP. This is particularly important for the detection of MDR, since MDR-TB is defined as *M. tuberculosis* which is resistant to at least INH and RMP.

If a SRL does substandard work, then its evaluation of the accuracy of the NRLs covered may be incorrect. Whenever a new SRL is added to the network, its performance must be evaluated before it can support national surveys. If a survey must be started in a

region without an established SRL, it is wise to collaborate with an established SRL elsewhere. This must be balanced with feasibility and the extra cost associated with mailing samples to a more remote laboratory.

In summary, quality assurance is necessary for the adequate performance of mycobacteriology laboratories conducting DST. Both quality control (i.e., inside the laboratory) and proficiency testing (external evaluation) are essential to improve quality assurance. When future surveys are planned in a given country, the assigned SRL should first conduct proficiency testing. SRLs and NRLs should develop a scheme for quality control[46]. When a NRL does not exist or its DST performance remains suboptimal, strains should be tested at the SRL itself.

In addition to the accuracy of DST, quality control also needs to emphasize safety in the laboratory. Biological safety cabinets built to internationally recognised standards (class I or II) are an absolute requirement whenever work is done with pure cultures, and particularly with aqueous suspensions. For international transport of strains, adherence to international regulations is mandatory[52,53,54].

4.3.2 Technical aspects of laboratory DST

One of the important findings of the Global Project, is that all four laboratory methods for DST can achieve similar levels of accuracy. Standard and economic variants of the proportion and the radiometric BACTEC 460® methods yielded similar DST results, both between and within laboratories, for the anti-tuberculosis drugs evaluated. These findings justify the continued use of traditional DST methods in institutions familiar with them or unable to afford more recent technology.

The three rounds of proficiency testing of the SRL network showed that laboratory performance can be improved and is important to maintain improved standards.

Important laboratory issues

- The global network of SRLs is a model for surveillance of drug resistance.
- Quality assurance is both essential and feasible.
- DST for INH and RMP is accurate.
- Regional networks may be advantageous.

Good sensitivity and specificity were obtained for both INH and RMP almost from the outset. Most of the anomalous results for INH were caused by reference test strains that were borderline resistant (one or two of the ten-strain panel, unchanged over time). This was not a problem for RMP. Borderline strains are infrequent in clinical practice (1% or less of resistant strains show borderline values). While it may be an occasional problem with an individual strain, the impact of this factor in ascertaining prevalence of drug resistance is minimal.

Standardisation of DST for SM and EMB was inadequate before the quality assurance programme was implemented throughout the SRL network. Because of insolubility, both SM and EMB need to be converted into salts (sulphate and chlorhydrate respectively) for DST. Since the drug is diluted, some laboratories correct for loss of

potency. In North America this is done only for SM, while in Europe it is generally, but not always, done for both SM and EMB. Some laboratories even used different correction factors. Substandard performance, however, was more often linked to departures from internationally standardised procedures as defined in the Guidelines.

Problems with the drug concentrations used and the time frame of reading were discovered. Cut-off criteria were not important contributors to interlaboratory discrepancies. Culture media and drugs from different manufacturers and of unstandardised quality could give additional problems. In one instance the L-J culture media had been prepared with quinolone-contaminated eggs. Many of the limitations in the SRL network were identified and overcome before NRLs were supported during country surveys. The few laboratories initially lagging in performance had improved by the third round with the help of simple, confidential feedback. As laboratories adopt international criteria and use equivalent reagents, the remaining problems in DST should decrease.

During this first phase of the Global Project only four drugs were evaluated. Additional studies are needed to standardise and ascertain the accuracy of DST for drugs such as PZA. DST of INH and RMP, at a minimum, and of EMB and SM, when feasible and accurate, is adequate in most situations and for most purposes. Given their importance in the treatment of patients and the excellent DST accuracy obtained in most settings, these four drugs remain the most appropriate targets for surveillance of resistance.

4.3.3 Regional networks for anti-tuberculosis drug resistance surveillance and quality assurance of local laboratories

For efficient implementation of a Global Project, several regional networks should ideally be set up to carry out technical exchanges between the participating countries in the region. The geographical proximity and cultural similarity facilitates technical exchange and collaboration to implement local surveys. The regional offices of WHO could play a critical role in the development of these networks by identifying target countries and experts in the region.

The experience so far of some regional networks suggests that the following issues should be taken into account when drug resistance surveillance is organised. First, surveillance within a country should be implemented independently at the state or provincial level if the number of TB patients, or geography, make it difficult for one central unit. For example, it is not feasible for one NRL in China to implement drug resistance surveillance for the whole country. When provinces within a country have their own reference laboratory for DST, sputum culture and DST can be done at that level and results reported to the national coordinator.

In some countries, the supervision and quality assurance of tuberculosis laboratories take place at peripheral and intermediate levels operating under the control of the NTP. In other countries, these activities are operated by an independent technical or administrative channel. In the latter case, a strong commitment by the NTP director or national coordinator is required to secure the administrative and technical link between the diagnostic centres and NRL.

The laboratory procedures in current use, particularly DST methods and the criteria for resistance, may vary greatly from country to country and even between different laboratories in the same country. Some countries perform DST for all new as well as old cases. A surveillance programme can easily be established in these countries if

results are comparable to those obtained by internationally accepted DST methods and resistance criteria. Drug resistance surveys should not start before the proficiency of the laboratory is considered adequate.

An organisation of NRLs and SRLs in the Pacific Region was set up, modeled after the Global SRL Network, by the Western Pacific Regional Office of WHO. The Korean Institute of Tuberculosis (KIT) carried out a quality assurance study on DST twice in 1995 and 1996, in which the NRLs of China, Hong Kong, Malaysia, Thailand and Vietnam participated. The results of the first round of proficiency testing, implemented by the Research Institute of Tuberculosis in Tokyo and the KIT in Seoul, showed a fairly acceptable concordance for susceptibility testing. Three NRLs showed an unacceptable concordance rate (<80%) for RMP resistance on the first round of testing, but improved considerably (93-100%) on the second round. All the participating NRLs showed an acceptable concordance rate for INH susceptibility testing on both rounds of proficiency testing. Additional improvement in DST proficiency is expected as the quality assurance at the regional level continues.

4.3.4 Developments in molecular techniques

Although the Global Project almost exclusively used conventional epidemiological and laboratory methodology, there have been recent developments in molecular technology applicable to DST and the epidemiology of MDR-TB. Current tests can rapidly and directly ascertain the drug susceptibility status of a given strain in clinical specimens without culture[91]. We have learned that the same genetic mutations underlie primary and acquired drug resistance, whether in isolates from AIDS patients or others, from lung cavities or extrapulmonary sites, and from Europe or sub-Saharan Africa[91,92].

At present, PCR-based tests are used only in speciating smear-positive specimens, and the results must be examined in the clinical context. The current limitations and expense associated with this technology prevent its use in routine clinical practice. PCR-based amplification of specific genes involved in resistance to individual anti-tuberculosis drugs is still in the future.

An easier approach is to detect growth of *M. tuberculosis* in the presence of a given drug using mycobacteriophages (viruses that infect specific mycobacteria)[93]. The phage-based PhaB assay is a recently introduced modification of the classic proportion method for DST. This technique is simple, relatively inexpensive and fast (3 to 4 days for results), and is as sensitive as PCR. While these methods are promising for RMP-DST they have not been tested in field situations, and standardisation is required before they can be used outside research laboratories.

Molecular techniques are also improving our understanding of the epidemiology of tuberculosis and drug resistance[94]. Specific strains of *M. tuberculosis* can be identified by restriction fragment length polymorphism DNA fingerprinting[95,96]. Clustering of strains sharing a DNA fingerprint is interpreted as suggesting an increased probability of recent *M. tuberculosis* transmission[97,98].

DNA fingerprinting has permitted a refined description of point-source tuberculosis outbreaks[2] as well as the routes for dissemination of specific drug-resistant strains[82]. This molecular tool has also documented exogenous reinfection, as opposed to tuberculosis relapse, in some settings[3], while ruling out exogenous reinfection in cases developing RMP resistance after rifabutin use[99].

Finally, clustering of DNA fingerprints is helping us re-examine the century-old debate about recent transmission versus reactivation of latent infection in tuberculosis epidemiology[2,3,100,101]. Molecular tools can provide a better definition of the two components in settings with different rates of TB infection. Recent transmission in New York, for example, has been estimated to be responsible for up to 40% of incident tuberculosis cases in five hospitals[2,3,102]. While these particular estimates may be explained by nosocomial transmission among HIV-infected individuals, further refinements and simplification of this methodology promise a better resolution of MDR-TB dynamics and epidemiological predictions of tuberculosis worldwide[94].

4.4 DEFINING DRUG RESISTANCE

Before the publication of the WHO/IUATLD Guidelines for Surveillance of Drug Resistance in Tuberculosis, there was no consensus on definitions or terminology in the field[18,62]. The controversy over the theoretical and pragmatic approaches to defining primary and acquired drug resistance is genuine, and the correlation between in-vitro drug resistance and clinical outcome needs more study. However, the consensus achieved by the Working Group permitted the standardisation of concepts and the methodology to ascertain them.

4.4.1. Primary drug resistance

Following the WHO/IUATLD Guidelines, we defined *primary resistance* as the presence of drug-resistant *M. tuberculosis* in a patient with no, or less than one month of, previous anti-tuberculosis drug treatment[46]. While theoretically simple, the definition usually relies on the patient's history, and the accuracy of gathering evidence of prior treatment varies from one setting to another. Because of this practical limitation, the term initial drug resistance was proposed for all cases admitting to less than one month of prior treatment without further attempts at verification. However, the systematic use of this alternative concept may discourage a thorough investigation into the history or documentation of prior treatment. For this reason, we support the use of 'primary drug resistance' as the best approximation to the true parameter of interest (i.e. infection by a resistant strain)[60].

4.4.2. Acquired drug resistance

Acquired resistance is found in a patient who has previously received at least one month of anti-tuberculosis treatment. The term "secondary resistance" was used in the past for the same situation. The one-month cut-off is not arbitrary. The slowly-growing *M. tuberculosis* almost never develops resistance within a month of drug treatment[24]. Drug resistance in a patient with only two or three weeks of treatment is most likely primary. If a cut-off point of more than one month were used instead, many patients who develop drug resistance during treatment would be incorrectly classified as having primary resistance.

While a one-month threshold virtually guarantees 100% sensitivity, the specificity of the definition may suffer for two reasons. First, for practical reasons, the current definition does not distinguish whether a patient had actually received the specific drug to which resistance is detected in the retreatment episode and for how long and/or how

many times. Second, some patients (over 50% in New York City, 1991)[8] may have been originally infected (or even recently reinfected) with a resistant strain of *M. tuberculosis* (i.e., they have primary drug resistance). In theory, such cases fall into a definitional vacuum or could have mixed drug resistance (i.e. infected with a resistant strain and then developed resistance to an additional drug). In practice, results of drug susceptibility tests in the original, sometimes remote, episode are almost never available.

In any case, the prevalence of acquired drug resistance will be inflated by the prevailing levels of primary drug resistance. That is, drug resistance in previously treated patients reflects both the rates of primary drug resistance prevailing when originally infected plus the resistance developed during the course or courses of anti-tuberculosis treatment. The further stratification of retreatment patients into different clinical subsets is important. Although the genetic mechanisms involved in primary and acquired drug resistance are the same, both the prevalence and the degree of acquired drug resistance increase with the duration of prior treatment and the number of treatment episodes received. Clinicians could thus expect different levels of drug resistance in patients returning after default and in those with relapse.

4.4.3. Combined drug resistance

Despite the importance of distinguishing primary and acquired drug resistance, we have also used the *combined (crude) prevalence of drug resistance* as an additional epidemiological parameter. This estimate represents an approximation to the proportion of all drug-resistant strains infecting individuals in a community at a given time. Combined drug resistance estimates are less vulnerable to the practical problems of ascertaining the history of previous treatment in individual patients and may provide a reliable estimate over time. Moreover, except in countries with a high proportion of retreatment cases (e.g. >10%), combined drug resistance was similar to the rates of primary resistance.

4.4.4. Acquired MDR Index

Acquired drug resistance only describes a small part of the problem. Individual retreatment cases have high drug resistance levels regardless of NTP's performance. For example, an NTP may be doing an excellent job, as in Korea, yet a few incurable cases persist with a high prevalence of acquired MDR (28% in Korea vs the median of 12% for the countries and regions in this report).

An alternative parameter, the Acquired MDR Index, is the number of patients with acquired MDR divided by the total number of patients presenting for treatment, which combines in a single estimate the proportion of retreatment cases and the rates of acquired drug resistance. We found the Acquired MDR Index correlates closely with the level of implementation of TB control according to the WHO monitoring system and with the retreatment proportion of registered tuberculosis patients. This parameter also correlates with the levels of primary drug resistance.

In summary, we recommend adherence to the WHO/IUATLD Guidelines in defining primary and acquired drug resistance according to patients history of anti-tuberculosis treatment[46]. The principles are clear and consistent with current recommendations for standardised therapeutic regimens[28]. At the same time, combined

prevalence can be estimated. The Acquired MDR Index is proposed as an additional parameter for monitoring NTP performance.

4.5 ASSOCIATION BETWEEN CLINICAL/DEMOGRAPHIC CHARACTERISTICS AND THE PREVALENCE OF DRUG RESISTANCE

4.5.1 The importance of age-specific information on drug resistance prevalence

From a public health point of view, the prevalence of drug resistance in younger age groups provides more reliable information on *current* transmission of drug-resistant TB, than in older people[103].

Combined drug resistance prevalence may not accurately reflect the strains currently circulating in the community because the incubation period between acquiring tuberculosis infection and developing clinical disease is variable. Primary anti-tuberculosis drug resistance in young children is therefore probably a better estimate of such dynamics[103], provided the children tested are randomly exposed to those with smear-positive tuberculosis.

Age-specific information may further refine our understanding of the dynamics of tuberculosis transmission. On average, patients developing tuberculosis in their thirties will have acquired the infection that led to disease earlier than patients in their twenties. Thus, the age-stratified prevalence of drug resistance may be an indicator of trends of drug resistance over time. For comparison of drug resistance levels between countries, adjustment for the age structure of the tuberculosis patient population might be necessary.

Empirical analysis of individual patient data was beyond the scope of this monograph. Levels of primary drug resistance in France 1962-1970 were less than 8% among patients 50 years or older, but more than 12% among 15 to 19 year olds[104]. A recent re-evaluation of these results estimated that only one third of the new cases of tuberculosis represented reactivation of remote latent infections: even among patients over 50, who are likely to have been infected earlier in the century, the majority were apparently reinfected by strains circulating after the introduction of SM and INH[105].

While the age-specific prevalence of drug-resistant tuberculosis provides useful information, there are practical limits to gathering sputum for culture in children, and HIV may be a confounding factor in some settings. Where available, however, rates of primary drug resistance among representative young children may provide the best estimate of the rates of drug resistance in the broader community[106].

4.5.2 Association between MDR-TB and HIV infection

UNAIDS estimated that 22 million adults were infected with HIV by mid-1996[107]. Over 90% of infections take place in the developing world[76] where 98% of TB-related deaths also occur[76,108]. Since an estimated 40 to 50% of the population aged 15 to 49 years in developing countries are latently infected with tuberculosis[76,108,109,110], about 9.5 million persons may currently be dually infected. Nearly 70% of those, or 6.6 million, are in sub-Saharan Africa. These people are at very high risk of developing active TB[111]. The association

is also well documented in the USA[112,113] and Europe[77,114,115,116]. The risk of developing TB among co-infected people is approximately 5-10% per year[117,118,119,120,121] compared to a life time risk of 5-10% for those infected with *M. tuberculosis*, but without HIV[122,123].

While the emergence of MDR-TB preceded the HIV epidemic, the problem of drug resistance was highlighted by outbreaks of MDR-TB among HIV-infected patients first in the USA[4,5,6,7], and then in some European cities[10,11,12,13]. These outbreaks, occurring mainly in nosocomial settings, were associated with delays in diagnosis, and high case fatality rates[9,81,124]. More recently, an increased prevalence of MDR-TB has been documented in HIV-infected people in community-based studies throughout the United States, independent of geographic location, history of prior therapy, age or race[36]. A report from San Francisco documents that AIDS patients with tuberculosis caused by fully susceptible *M. tuberculosis* have a higher risk of relapse with drug-resistant disease than other patients[125]. Studies in other countries however, have not found an association between HIV-infection and MDR-TB[126]. A common denominator for the association to occur has been the combination of increasing MDR-TB incidence in populations with relatively low prevalence of TB infection.

Patient-related factors in MDR-TB

- Age-specific information may help understand the dynamics of MDR-TB transmission.
- The association between HIV infection and MDR-TB is inconsistent but may reflect selective exposure in areas with increasing MDR-TB.
- Information on country of birth is important in understanding MDR-TB levels in both the host and the country of origin.

The Global Project did not specifically test the association between individuals with HIV and MDR-TB, but no correlation was found at the ecological level. In fact, the countries with the highest HIV seroprevalence among tuberculosis patients (those in sub-Saharan Africa), generally had a low prevalence of MDR-TB; the opposite occurred in Eastern Europe.

Only two countries provided comparisons at the individual level. Previous results from the United States are well publicised[113,117,118]. The survey in the Ivory Coast found no association between HIV and MDR-TB, but in Argentina it did. In the Ivory Coast, where TB transmission was high, patients probably reactivated *M. tuberculosis* strains acquired in childhood and with similar drug resistance patterns regardless of HIV status. In Argentina, as it occurred in New York City around 1990, HIV-infected patients may have acquired MDR-TB as adults, particularly in hospitals.

The transmission of MDR-TB is not restricted to HIV-infected patients, nor to nosocomial settings[36,80]. HIV-negative patients with MDR-TB are more often sputum-smear positive than HIV-positive individuals, and they are also less likely to die[34]. Thus, HIV-negative MDR-TB cases may be more likely to spread the disease among their contacts. However, outbreaks of MDR-TB among HIV-infected patients have significant public health implications, requiring investigation of the causes and prompt interventions. Nosocomial outbreaks also highlight the importance of hospital infection control policies

in the fight against the spread of MDR-TB[127,128]. TB patients should receive the same initial treatment regimen regardless of HIV-status[28,129,130].

4.5.3 Migration and other social and political factors in the genesis and interpretation of anti-tuberculosis drug resistance

Tuberculosis is a classic example of medical conditions intertwined with poverty and other socioeconomic circumstances. This is illustrated by the resurgence of tuberculosis in eastern Europe, with high mortality rates and the emergence of MDR-TB. However, as illustrated by New York during the 1980s, poverty and poor treatment of tuberculosis may occur even in the richest countries[131,132]. The common denominator is the disruption of appropriate control measures.

During the survey in Sierra Leone, 20% of the country was controlled by the rebel forces. With support from the Armauer Hansen Institute in Germany, a survey was conducted in 80% of the country, randomly sampling 15% of all smear-positive cases. Sierra Leone reports 'good' performance indicators: standardised regimens, use of FDC tablets, and initial treatment under direct supervision. Yet 30% of new cases were found to harbour organisms resistant to at least one drug; 1.8% had MDR-TB, even though RMP had only been recently introduced. The ongoing war may have contributed to this situation.

Human migration has shaped the history of disease and emphasizes the global nature of transmissible conditions such as tuberculosis[133]. Furthermore, international markets and tourism have accelerated human movement and its associated health hazards; air travel has increased almost 20-fold since the 1960s. The movement of people is likely to increase even further in the future. Tuberculosis can be transmitted in airplanes[134] or in any other indoor setting where people meet. The risk of travelers being infected with a potentially incurable, multidrug-resistant strain of the disease will also increase.

As demonstrated in the Global Project, the prevalence of drug resistance is geographically heterogeneous. Systematic surveillance in the United States has also demonstrated dramatic differences from one region to another[17], and urban and rural settings have differences in the levels of drug resistance as well[135]. MDR-TB is more common in certain social groups[136]. Thus, there are gradients in the prevalence of drug resistance, country borders are not necessarily involved, and human movement along such gradients spreads MDR-TB.

The impact of migration along gradients of drug resistance, and its consequences for tuberculosis control, depend on: i) the direction along the gradient and the magnitude of the flow; ii) the specific type of drug resistance; iii) the burden of tuberculosis and the levels of drug resistance in the country of destination; and iv) the financial and technical capabilities of the NTP in the receiving country[79]. In general, only migration from areas with high levels of drug resistance to regions with significantly lower rates (and sometimes less experience in managing TB) is epidemiologically relevant. However, the socioeconomic status of migrants may be more important than their country of birth.

Reliable data on migration and drug resistance are limited, especially in the southern hemisphere, and drug resistance rates are rarely stratified according to place of origin. In Australia, Canada and several European countries more than 50% of tuberculosis cases occur in people born elsewhere[76,77,78,137]. Several studies in those countries have documented higher rates of drug resistance among foreign-born patients[30,138,139,140,141]. The same phenomenon is reported in Saudi Arabia[142], and the association between tuberculosis

and immigrants is well known in North America[30,113,143,144]. An analysis of the resurgence of TB in the United States attributed 60% to immigration[113], although the effect of poverty was not analysed and some studies have not found higher MDR-TB levels in US immigrants[17]. On the other hand, the highly resistant strain W that originated in New York spread not only to neighbouring states[82] but also to Paris.

4.6 IMPACT OF ANTI-TUBERCULOSIS TREATMENT STRATEGIES ON THE PREVALENCE OF DRUG RESISTANCE

4.6.1 Standardised Short Course Chemotherapy (SCC)

The strategy for control of tuberculosis adopted by WHO and IUATLD[59] is based on five elements as described in section 2.10.1. A crucial component of the strategy is the provision of standardised SCC to all smear positive cases under direct supervision. This recommendation is based on the principle that haphazard variations in patient management are the source of poor control[59]. In most countries, the uncontrolled multiplication of regimens prevents the rational procurement and distribution of drugs, and, the cost of non-standard regimens may be higher than that of the standard, effective regimens that WHO and IUATLD recommend.

Country-wide standardisation of anti-tuberculosis regimens, together with adequate drug supply and health care infrastructure, has been associated with protection against the development of drug resistance in both developing and industrialised settings. For instance, the introduction of standardised SCC in 1986 in Chile was followed by a reduction in the prevalence of acquired resistance[145]. The stable level of 10% primary resistance, however, prompted the use of four drugs in the initial phase of treatment to reduce this level of resistance. In Algeria, the introduction of standardised 12 month regimens after 1967 produced a rapid decrease in the prevalence of both acquired (from 82% to 61.5%) and primary (from 15% to 10%) drug resistance. With the introduction of standard SCC in the mid 1980s, the prevalence of drug resistance was further reduced to 21% (acquired) and 5.2% (primary) in the late 1980s[146]. This was achieved in the absence of a programme of direct treatment observation.

In industrialised countries, the impact of sound treatment policies has been demonstrated in places like New York[132,147,148]. Nineteen per cent of all culture-proven TB cases in New York in April 1991 were found to be resistant to both INH and RMP[8]. A major reorganisation of the TB control programme followed together with an influx of the necessary resources. The annual number of cases of MDR-TB fell by 75% between 1992 and 1995[106]. This reduction in just three years is the most convincing evidence to date that programmatic improvements can have a major impact on the epidemiology of MDR-TB[149].

In the Global Project, all countries surveyed claimed to recommend standardised treatment regimens. However, in a few countries, such as those of the former Soviet Union, a variety of individualised regimens was used until very recently[83]. This factor, and the erratic drug supply, may have contributed to the high level of drug resistance observed in Latvia, Estonia, and the Ivanovo Oblast, Russia. Non-standardised treatment regimens are an important contributor to the high prevalence of drug resistance found in New Delhi.

4.6.2 Impact of direct observation of treatment on drug resistance prevalence

In the Global Project, we found no consistent association between patterns of directly observed therapy and the prevalence of drug resistance, because the observations were limited in number, imprecise, and not in the appropriate timeframe. However, Botswana, Cuba[150], and the Czech Republic, countries which for a number of years have provided fully observed treatment in the majority of cases in the context of sound TB control programmes, have some of the lowest prevalences of resistance. In the case of Peru, which also uses directly observed therapy, the higher prevalence of drug resistance is probably a residue of programmatic weakness before a sound TB control strategy was introduced in 1990.

Studies in Kolin, Czechoslovakia[151] and, more recently, in Baltimore[35], New York[148,149] and Texas[152] have shown that directly observed therapy has a positive influence on the level of drug resistance[153].

The suggestion that treatment under direct observation helps to protect against the development and spread of drug resistance is therefore difficult to question, and this policy may be cost-effective[154,155,156]. Implementation of this strategy, however, has been slowed by ethical concerns about discrimination and logistical limitations in rural areas[157]. In addition, while directly observed therapy is effective[85], it is not clearly necessary in all settings. Countries, such as Korea and Algeria[146], achieved a low prevalence of resistance by implementing sound TB control without directly observed therapy.

TB treatment strategies and MDR-TB

- Standardised SCC was associated with lower levels of MDR-TB.
- No significant correlation demonstrated for directly observed therapy and use of fix-dose combination tablets. Better evidence is needed.
- The impact of TB treatment in the private sector remains to be elucidated.

4.6.3 The potential benefit of using fix-dose drug combination tablets

If anti-tuberculosis treatment cannot be provided under direct observation, FDC tablets may help to prevent inadvertent monotherapy[158]. The use of FDC tablets, recommended by both WHO and IUATLD since 1988[159], is based on the rationale that they ensure polychemotherapy and enhance treatment adherance[160,161]. When used appropriately, FDC tablets should decrease the risk that MDR-TB will develop[162]. FDC preparations, however, do not guarantee patient adherence, and low quality preparation[163] or subtherapeutic doses could still lead to drug resistance.

Although difficult to separate from other factors, we analysed the impact of FDC tablets on the prevalence of drug resistance. The limitations of this analysis, however, must be acknowledged. Besides the small number of countries available for the ecological analysis, measurement of the use of FDC tablets is often problematic. In countries where anti-tuberculosis treatment is available in the private sector, quantifying the actual use of different preparations is difficult. Thus, this analysis should be interpreted with caution.

In the Global Project the degree of use of drugs dispensed in FDC was not correlated with the prevalence of drug resistance. Nevertheless, most countries providing

anti-tuberculosis drugs as FDC tablets to over 95% of TB cases (Brazil, Lesotho, New Zealand, Scotland and Swaziland) reported very low levels of drug resistance and MDR. A notable exception is the Ivanovo Oblast, Russia. But there, FDC tablets were introduced only in late 1995, as part of a WHO pilot project.

On the other hand, some countries with no FDC tablets available (Botswana, Cuba, Nepal, Korea, Zimbabwe) also had low levels of MDR. The success in preventing the emergence and spread of resistance to RMP may be due to a combination of factors including directly observed therapy, standardised regimens, and the unavailability of drugs outside the programme. Additional evidence is needed to clarify the impact of FDC tablets in controlling drug resistance.

4.6.4 The impact of treatment in the private sector on anti-tuberculosis drug resistance

One of the main tasks of an NTP is to ensure that diagnostic and therapeutic policies are followed throughout the country, including the use of recommended standardised treatment regimens. In many countries where the private sector, both for-profit healthcare providers and non-profit organizations, is well established, many patients seek care through a private practitioner[164], and completely bypass the public sector . This hinders surveillance and therefore, reporting. More importantly, the treatment of tuberculosis patients may be chaotic, with prescription of unnecessarily long, expensive, and/or inadequate regimens[164]. The private sector is also associated with the availability of drugs in private pharmacies. Patients may purchase only some of the drugs due to lack of money, leading to monotherapy and irregular treatment. Increased failure and relapse rates and, ultimately, the emergence of MDR-TB may occur. The high prevalence of MDR-TB in Delhi (India) is probably due in large part to these practices within the private sector.

The analysis of the data obtained through the Global Project found no correlation between the percentage of patients receiving anti-tuberculosis treatment within the private sector and the prevalence of drug resistance. Half the surveys in this report targeted solely patients in the public sector, who may or may not have the same levels of anti-tuberculosis treatment as those seen by private practitioners. In addition, 'the private sector' means different things in Russia, India or the United States[165]. Effective TB control, depends on both the adequate training of private health providers and the quality of the public health programme.

4.7 DRUG RESISTANCE AS AN INDICATOR OF NTP PERFORMANCE

Several indices for evaluating the status of the tuberculosis epidemic have been used during the century, each having its limitations. In countries with mandatory reporting and formal surveillance systems, tuberculosis case notifications can be easily monitored. However, the majority of countries lack such systems, with less than a third of the estimated number of smear positive cases being notified[63]. Even in industrialised countries, case notification rates are only a rough indicator of the recent performance of tuberculosis control programmes because of the delay between infection in the community and clinical reactivation of the disease. Case fatality has similar limitations[166,167,168,169,170].

The annual risk of infection with *M. tuberculosis* in a community, defined as the proportion of the population that becomes infected in the course of a year, is a good

indicator of the tuberculosis situation in a given country or region[122,171]. Unfortunately, measuring this indicator requires large, expensive periodic surveys using tuberculin skin testing, which may be inaccurate.

The performance of the NTP has also been judged through programmatic indicators such as the cure rate among smear-positive cases of tuberculosis. While conceptually simple, official notifications and documented cure rates vary widely, depending on the quality of health services and the monitoring and reporting systems. Furthermore, early deaths in elderly or HIV-infected patients limit the accuracy of this parameter in some countries.

Can we use drug resistance, in some way, to indicate aspects of the performance of TB control? Anti-tuberculosis drug resistance develops almost exclusively after inappropriate treatment[172], which occurs both within NTP clinics or in unregulated private sectors, and independent of the official detection or notification of cases. Once acquired resistance develops, then the rest of the population is exposed to, and some are primarily infected with, resistant strains. Thus, the prevalence of drug resistance is an indicator of the overall quality/effectiveness of national or regional tuberculosis treatment[173]. However, the relationship between drug resistance and the quality of an NTP is complex.

4.7.1 Factors modifying the association between drug resistance prevalence and NTP performance

There are at least three important modifiers of the association between drug resistance levels and NTP performance: exposure to the drug, socioeconomic conditions, especially migration, and the time taken for control modifications to have an effect. First, clinical drug resistance will not develop unless patients are exposed to the drugs. Areas not using RMP will not see native cases with MDR-TB.

Second, the socioeconomic factors discussed in section 4.5 may confound the association between drug resistance prevalence and NTP performance in a given country or region. The poor, ethnic minorities, the homeless, alcoholics, substance abusers, prison inmates, those living in overcrowded conditions or with limited access to the healthcare system, are less likely to receive treatment to completion[33] and more likely to develop drug resistance[34], thus contributing to the spread of MDR-TB[8,82]. While New York is a prime example of synergistic interaction between the socioeconomic characteristics of the population and the quality of the TB control programme, similar dynamics occur elsewhere.

The migration of people across 'borders'(see also section 4.5.3) is particularly important in countries receiving large numbers of immigrants from countries with a higher prevalence of tuberculosis and poorly performing NTPs[78,174,175,176]. Drug resistance levels may then reflect tuberculosis control performance elsewhere. In the Netherlands, for example, 82% of 809 bacillary tuberculosis patients with drug resistance in 1993 were foreign born. Collection of data on country of birth, the date of immigration (the rates of drug resistance are different in those who have lived in the host country for less than two or three years), and differentiating between asylum seekers and other migrants, will help disentangle this issue.

A third factor in judging the performance of NTPs by the prevalence of drug resistance is the time lag between changes in TB control and their impact on drug resistance prevalence. High levels of primary MDR-TB reflect a chain of events starting from the inclusion of INH and RMP into anti-tuberculosis regimens, the inappropriate prescription of these medications or poor adherence to treatment, the development of

acquired drug resistance, transmission to other people in the community, and, finally, the progression to or reactivation of clinical disease. To date, we have ignored the length of time between the start and finish of this sequence of events. The 75% reduction in MDR cases in New York from 1992 to 1995 suggests that it is not necessarily long, especially among HIV-infected people (who progress to clinical disease quite rapidly). Focusing on drug resistance levels in young people is likely to reflect more recent NTP performance (see Section 4.5.1).

4.7.2 Which drug resistance parameter best indicates the performance of NTPs?

In evaluating NTP performance based on prevalence of drug resistance, the question is which of several possible parameters can best fulfill this task. Should we use specific (single drugs, primary or acquired) or aggregate (any drug, MDR-TB, combined prevalence) estimates, and actual rate or ranges (e.g., terciles of primary MDR-TB prevalence <1%, 1-2%, and 2%)? Most of our analysis and discussion focuses on MDR-TB, rather than on individual drugs or other patterns of drug resistance, because of its threat to the successful treatment of individual patients with SCC. The following discussion of the relative merits and limitations of the different parameters complements the discussion of definitions in section 4.4.

Traditionally, programme performance has been indicated by the proportion of drug-resistant patients among new and retreatment cases, which parallels the recommended algorithms for standardised treatment regimens[28]. High levels of primary resistance suggest transmission of *M. tuberculosis* resistant to drugs has been occurring in the community[62]. Trends of primary resistance over time represent an excellent way to monitor NTP effectiveness (as documented in Korea, Texas and New York), as long as survey methods are consistent. This parameter, however, is an indicator of NTP performance over several years and may not reflect the current quality. Peru, for example, has implemented a model TB programme since 1991. Despite current success, MDR-TB levels are relatively high (although probably declining). High levels of primary resistance, on the other hand, may also indicate misclassification of some previously treated patients. Combined estimates of drug resistance ignore the history of previous treatment and the accuracy of patient information but they obscure the different mechanisms leading to primary and acquired resistance.

Resistance among previously treated patients can be estimated more accurately than primary drug resistance. As drug resistance is a consequence of poor treatment, high levels of acquired resistance should indicate poor programme performance in the recent past. However, only some of the resistance observed in retreatment cases is truly acquired, a fraction of such patients having been originally infected with a resistant strain and having had primary drug resistance in the first episode of their disease.

More importantly, the proportion of retreatment patients harbouring resistant strains will usually be high regardless of the quality of NTPs. As these frequently recalcitrant patients experience additional waves of treatment, their degree of resistance increases[19]. Thus, it is possible to have almost 100% acquired drug resistance in an otherwise excellent NTP, such as in Cuba and Korea[85,150]. The key to this apparent paradox is the fraction of patients in the programme that follow this path. Countries like Cuba or Korea have few retreatment patients, thus the absolute number of acquired drug-resistant cases is small.

To capture the relative importance of both factors we calculated the Acquired MDR Index dividing the number of retreatment cases with MDR-TB by the total number of patients in the programme. This parameter is epidemiologically sound and correlates very well with the TB control categorisation of countries according to WHO; it also correlated with the prevalence of primary drug resistance. The estimated Acquired MDR Indices for Cuba and Korea were only 0.4% and 1.7%, respectively, despite these countries having acquired drug resistance prevalences of 91% and 53%; by comparison, the Acquired MDR Index in Latvia was 10.5%.

4.7.3 Drug resistance levels for monitoring NTP performance, and comparison with other indicators

Can drug resistance levels be estimated in countries or regions in a simple, inexpensive but reliable way? Does the information so gathered add to the more traditional indicators of NTP performance?

The Global Project made it clear that, despite some limitations, standardised laboratory measurements can be made in countries throughout the world. However, epidemiologically sound drug resistance surveys are not a simple matter; they involve major mobilisation of resources, and some surveys cost several hundred thousand US dollars. Some countries were unable to carry out their plans for surveys because of logistic limitations, despite the technical and partial financial support provided by WHO. Thus, while feasible in many countries, in others drug resistance surveys may require much more support to be successful. Routine implementation of such surveys to monitor NTP performance may not be possible in some settings.

Drug resistance surveillance cannot replace the traditional parameters of NTP performance described at the beginning of section 4.7. On the other hand, drug resistance levels may provide a summary of complex transmission dynamics and may furnish information that routine cohort analysis does not. Moreover, high resistance levels not only indicate deficiencies in a TB control programme but actually galvanise a community into action[149]. People may be complacent about poor treatment success rates; however, they readily respond to the suggestion that their children may be infected with a potentially incurable disease.

Rational decisions concerning the number and types of drugs to be used in standardised regimen can only be made in the light of knowledge of drug resistance patterns. Thus, periodic surveys are needed. Such surveys could focus on primary MDR-TB in children, which will better reflect the most recent trends, and on the Acquired MDR Index, if further work clearly demonstrates its usefulness. When resources are available, drug resistance surveys or on-going surveillance can be helpful additions to traditional indicators of NTP performance. At any rate, high levels of anti-tuberculosis drug resistance call for a formal evaluation and reorganisation of the TB control programme. Surveillance can be justified only if its results are followed by the necessary interventions[60].

4.7.4 Ongoing surveillance vs periodic surveys to monitor drug resistance

Drug resistance is almost inevitable whenever an antimicrobial agent is being constantly used. However, the emergence of resistance over time can be influenced by changes in the quality of TB control[35,86]. Examples of upward slopes are New York (during

the 1980s)[177], Djibouti and Thailand. Examples of downward slopes include Algeria, Korea, possibly Tanzania, Texas, and New York (during the 1990s). Since, there is always a time lag between TB control interventions and their impact on drug resistance levels, there is clearly a need to obtain serial information, with either repeat surveys or continuous surveillance[78].

In some national programmes the monitoring of trends, through periodic surveys, may be considered the best approach to resistance surveillance[86,178]. To observe trends proper sampling procedures are necessary, as described in the WHO/IUATLD Guidelines. The interval between repeat surveys would vary according to resources, but should not exceed five years since local expertise may be lost and dramatic changes in drug resistance may occur within that period[149]. As the levels of drug resistance go up or down, so should the frequency of surveys. If resources are limited, smaller, well-conducted surveys in sentinel groups may be an adequate alternative to large-scale projects.

In some countries, routine surveillance of anti-tuberculosis drug resistance may be feasible or preferred[179]. However, this approach is very costly and surveillance systems may not be sustainable in some settings. None of the surveys sponsored by the Global Project has so far led to the establishment of ongoing surveillance of anti-tuberculosis drug resistance. A third of the countries included, mostly in developed settings, had surveillance systems already in place. Thus, not all situations require the same approach and decisions on periodic surveys versus ongoing surveillance should be dictated by local circumstances.

4.8 IMPLICATIONS OF THE PREVALENCE OF DRUG RESISTANCE FOR THE TREATMENT AND CONTROL OF TUBERCULOSIS

MDR-TB, defined as resistance at least to INH and RMP, is a cause of great concern among tuberculosis experts and public health officials around the world. Not only does the emergence of MDR-TB signal that control strategies are failing; MDR-TB itself could become an obstacle to effective anti-tuberculosis treatment. TB patients with MDR strains require individualised and expensive treatment in specialised units[180]. Such patients are more likely to fail treatment and go on infecting others in the community. Many of them die as a result of MDR-TB[19].

However, these considerations are mainly based on anecdotal evidence, or small series of patients. Controversy remains about the precise effect MDR-TB has on the treatment of individual patients and on the control of TB in the community. The perspective of physicians caring for individual patients differs from that of TB control officers responsible for public health in rich or poor countries. Different components of the threat of MDR to TB control are reviewed here.

4.8.1 The virulence of MDR-TB

In the absence of definite clinical and epidemiological data, most discussion of this issue is based on indirect data and speculation. Population geneticists claim that burdening an organism with a large number of mutations carries a fitness cost. In other words, the selective advantage of resisting the actions of a specific drug is accompanied by a survival disadvantage in the absence of the drug[181]. If MDR strains are less virulent than drug-susceptible organisms, drug resistance would eventually disappear from the community (although not from individual patients) as long as no new MDR-TB was generated by

substandard therapy. Reduction in resistance did indeed occur in Algeria, Texas, Korea and New York, but only after the implementation of sound TB control measures[86,149,151,173]. The final characteristics and prevalence of drug resistance will be driven by selective pressures, such as the availability of drugs and patterns of drug use. Indeed, most evidence documents the emergence of anti-tuberculosis drug resistance throughout the world[45].

The question of how the clinical virulence of MDR organisms compares to that of drug-susceptible or monoresistant strains also arises. Given our understanding of the pathogenesis of TB, this question can be split into differences in the infectivity (i.e. ability to infect or colonise a host), the pathogenicity (i.e. ability to cause clinical disease) and the virulence (i.e. ability to cause serious damage or death). The infectivity of TB is measured by the proportion of people that convert their tuberculin status from negative to positive after exposure to an index case of active TB. While there are many factors that complicate this issue, there is no evidence to suggest a difference in the skin test conversion rate between contacts of cases with MDR-TB, and those without it.

The question of whether MDR infections progress to clinical disease faster or more frequently than drug susceptible ones has not been tested in any controlled manner. MDR-TB can be clinically explosive, particularly among HIV-infected persons, as in the nosocomial outbreaks in the USA[5,8]. Yet drug susceptible strains, while less eye-catching than MDR ones, also cause epidemics in settings with a high HIV incidence and little infection control. The death toll associated with MDR-TB is also well documented[9], yet it is difficult to dissect the case-fatality attributable to MDR-TB from HIV co-infection, delayed diagnosis, and inappropriate treatment of such cases[124]. While many have witnessed the clinical deterioration and death of patients with MDR-TB, the literature also documents one spontaneous recovery[182].

Soon after the introduction of INH, laboratory studies showed that drug-resistant strains were less viable in-vitro[183] and less likely to cause disease in experimental animals[181,183,184]. Previously, it had been shown that guinea pigs infected with strains of *M. tuberculosis* resistant to streptomycin survived longer than those inoculated with similar amounts of drug susceptible organisms. This biological disadvantage - attenuation of viability and virulence - was intimately associated with a genetic deficiency in catalase activity[183,184]. *M. tuberculosis* strains that have lost their catalase activity completely (and are highly resistant to INH) are virtually nonpathogenic[183,184]. Studies of patients with INH-resistant TB could not settle the matter. Since the strains infecting asymptomatic individuals are beyond the reach of clinical mycobacteriologists, and as the incubation period between exposure and clinical disease (the stage when DST can be performed) is long and variable, the question of whether MDR-TB is more or less likely to cause clinical disease in humans will remain unanswered until better technology is available.

Important epidemiological questions on MDR-TB

- How efficient is the transmission of MDR-TB compared to drug-susceptible strains?
- What is the clinical virulence of drug-susceptible versus MDR strains of M. tuberculosis?
- What is the impact of MDR on the cure and relapse rates of TB with standard SCC under programme conditions?

4.8.2 Historical perspective on the importance of drug-resistant TB for the control of the disease

Drug resistance appeared soon after the introduction of SM and INH for the treatment of tuberculosis[22,23,24,25,185]. Canetti, Fox and others soon realised the importance of adding a third drug, such as PAS or thiacetazone, to prevent the selection of INH-resistant bacilli. The use of SM during the initial phase of treatment was also found to be crucial for reducing the total number of bacilli as quickly as possible. During this early period, several surveys reported a low rate of acquired drug resistance[14,16,186].

A study in Madras (1960-63) showed that intermittent chemotherapy with INH and SM twice weekly (S_2H_2) was as effective as INH+PAS or INH+thiacetazone daily. The implementation of S_2H_2 regimens, either from the outset or after an initial phase of treatment with STH or SPH, produced excellent results (a failure/relapse rate of 10 to 15% after 3 years). However, unlike PH regimens, S_2H_2 was accompanied by a two-fold increase in the rate of acquired 'MDR' (before the RMP era the term was applied to simultaneous resistance to INH and SM)[187].

Primary anti-tuberculosis drug resistance emerged as an important problem at the end of the 1960s. Some experts suggested replacing PAS or thiacetazone with ethionamide or PZA. Workers in Hong Kong (1971-1972) sought to determine the impact of primary drug resistance on chemotherapy outcomes under programme conditions[188]. The study also evaluated the effect of changing the treatment regimens according to the results of DST. It was clear that DST results had little impact on the treatment regimen and that virtually all failures could be detected by monitoring sputum smear conversion.

The introduction of RMP around 1970 made shorter and more effective treatment regimens possible[189]. In a series of randomised clinical trials from 1972 to 1983, the British MRC established that SCC regimens have low failure/relapse rates (1 to 4% in 6-month regimens; 2 to 8% with 8-month regimens using RMP only in the first 2 months of treatment). In patients with primary drug resistance, failure rates were 5 to 10% with 6-month regimens and 15% with 8-month regimens (again using RMP only in the first 2 months). At the same time, 6-month regimens (with RMP throughout) had a higher risk of producing MDR among treatment failures (30 to 50% acquired MDR as it is now defined). Thus, only 0.3 - 2% of the patients acquired MDR, and this was more likely in patients with prolonged or recurrent RMP use[190,191].

4.8.3 The potential threat of MDR to TB control in the era of Short Course Chemotherapy

The true impact of MDR-TB on treatment outcomes in the era of SCC remains to be determined. This survey has demonstrated its existence in 34 out of 35 countries surveyed, but did not set out to measure the impact of drug resistance on TB control. But, since a single contagious patient infects on average one person a month[123], the potential of MDR-TB becoming a serious threat to TB control efforts is readily apparent. Relatively few effective drugs are available against *M. tuberculosis*, especially in low income countries[18,178,192], and the special treatment of patients with MDR-TB is much more toxic and expensive than the treatment of patients with drug susceptible strains[20].

However, many additional factors influence this simple logic. First, under programme conditions, SCC regimens using four drugs result in cure in a majority of patients[85]. Second, some new patients with low grade resistance may still respond

clinically[50]. Lastly, up to a third of TB patients recover as part of the natural history of the disease[168,169]. Such an outcome has been documented in MDR-TB[182]. Thus, empirical observations are needed to clarify the extent that MDR may compound the fight against TB.

The outcome of MDR patients can be poor. Mitchison and Nunn reviewed 12 controlled trials using SCC sponsored by the British MRC[50]. Patients with initial resistance to RMP did poorly, with 8 of 11 (73%) having unfavourable outcomes[50] despite high quality clinical management. However, these numbers are small. Resistance to all four first line drugs (as with strain W) is ominous, but it is also extremely rare in most countries (median value globally in new patients is 0.2%). Goble et al. reported a retrospective study of 171 patients with pulmonary MDR-TB, resistant to a median of six anti-tuberculosis drugs, seen between 1973 and 1983 in Denver: 63 (37%) died, despite expert management[19]. While HIV was not an important factor, only 37 of these deaths were attributed to tuberculosis and the group had previously failed to a median of six drugs. Similar results were reported in Rio de Janeiro[193].

In the presence of HIV, the outcome of MDR-TB is even worse (and vice versa)[124]. The nosocomial outbreaks of MDR-TB in the United States around 1990[5,7,194], due to delayed diagnosis[195], were associated with very high case-fatality rates[9,81]. Malnourished prisoners in developing countries also have a high mortality when MDR-TB emerges[196].

The treatment of nonchronic, HIV-negative patients with MDR-TB, but less resistance to other drugs than in the Denver study, is more straightforward when there is access to all available medical and surgical means: bacteriological conversion in over 90% of such cases was achieved with a combination of chemotherapy and resectional surgery[155] with only one death (a diabetic with renal failure)[182].

Treatment outcomes under programme conditions for patients with MDR-TB have been evaluated in the Masvingo Province of Zimbabwe[197]. Among 192 patients with drug susceptible tuberculosis (74% were HIV-infected and 9.4% had been previously treated) 3.6% failed to convert to sputum-smear negative after two months of treatment, 10.9% died and 73.9% completed treatment successfully under direct observation for at least two months (actual regimen not specified). On the other hand, in eight cases with MDR-TB the respective figures were 25%, 50% and 37.5%; in this group 50% were HIV-infected and 12.5% were retreatment cases. The number of cases is small and the contrasts do not reach statistical significance. Similarly, among seven patients with primary RMP resistance in the WHO Pilot Project in Ivanovo Oblast (Russia), one died and three others failed treatment.

At the programme level, however, the introduction of sound control programmes has been associated with a fall in resistance levels in Korea[86], Algeria[173], Texas[151] and in New York[106] where even MDR-TB case numbers fell.

In summary, MDR is a potential obstacle to the successful treatment of TB. However, the crucial empirical evaluation of this in large samples of new, HIV-negative patients is lacking. Where MDR is common, it is because of poor control, and failure rates in such settings will also be high for the majority of patients who have drug susceptible organisms. At the same time, experience around the world confirms that resistance levels in a given country can be reduced by the implementation of sound control policies[86,146]. Theoretically, however, there must be a threshold of MDR levels above which such policies will not work. Patients with MDR-TB are not so much a threat to a control programme as they are to themselves and their contacts and, where possible, should be treated by experts in an appropriate setting[172]. To the community, patients with drug susceptible TB pose a more common threat if not treated properly. Overall, resistance to

implementing sound control strategies is probably more of an obstacle in the fight against tuberculosis than MDR-TB.

Implications of MDR-TB for TB control

- Good TB control prevents or reverses high levels of MDR-TB in the community.
- MDR-TB is caused by erratic treatment; adding a fifth drug to initial regimens in such settings would not work and will lead to additional drug resistance.
- NTPs should be reorganised to guarantee SCC with four drugs for all new patients.
- Individual patients with MDR-TB should be referred for expert management.

4.8.4. Drug resistance and clinical management of individual patients

While MDR is not an insurmountable barrier to well-implemented TB control programmes, individual patients with MDR-TB face uncertain prospects of successful treatment[19,50,193], side effects from medication (when available), and the associated expense[20]. Confronted with a potentially fatal disease, clinicians are ethically compelled to offer every available treatment. However, good clinical practice should be influenced by the principle of *primum non nocere* (first, do no harm): antibiotic misuse underlies the emergence of drug resistance and cannot be justified by the (genuine) concerns of clinicians. In a programme context, futile efforts in a few incurable cases may only drain resources that could be used to cure many patients with drug susceptible TB and to prevent MDR-TB in the first place.

When treating individual cases there are two important decisions concerning drug resistance: whether or not patients should undergo DST routinely, and what is the most appropriate initial drug regimen. The answer to both questions depends on the resources available to the NTP. Routine DST for clinical management of all TB patients is simply out of the question in most countries. Furthermore, even when available, such results should not affect the regimen used to treat over 95% of tuberculosis patients. Failure to convert sputum smear positive to negative results after two months of the recommended four drug treatment would in fact coincide with the usually delayed DST results documenting the infrequent cases with primary MDR-TB. A careful investigation of prior anti-tuberculosis treatment is important to identify retreatment cases and the likely pattern of drug resistance[190,193]. Even in the absence of DST results, these patients would enter standardised protocols for treatment failure and, when necessary, would be referred for expert treatment[180].

Some experts argue that in countries with a high TB burden and few resources DST should only be done for surveillance purposes and not to guide therapeutic decisions about individual patients. In such countries, DST may distract from the essential duty to perform smear microscopy. Feedback of DST results to individual physicians may be futile where second line agents are not available or affordable. The results of DST in laboratories with a low volume of tests (e.g. <300/year) may not even be accurate[198]. More importantly, DST results may cause confusion and may only lead to inappropriate retailoring of therapeutic regimens without improving their efficacy (i.e., changing

standardised regimens in patients with INH or SM monoresistance)[20]. Poor implementation of recommended regimens may then lead to the therapeutic chaos in which MDR-TB thrives.

Specific retreatment regimens are recommended for patients who fail initial therapy. WHO recommends an 8-month regimen starting with five drugs (2SHRZE/1HRZE/5HRE) for use in countries without access to DST for individual patients[28]. The majority of these patients can still be cured if they are HIV-negative[182]. Patients whose treatment fails after two courses of the standardised regimen (the second being fully supervised) are likely to harbour MDR-TB (50% or more)[190,193]. Such cases should be referred to an officially qualified centre with the required expertise and exclusive access to second line drugs. A specialised unit may be regarded as an expensive luxury in some countries, but second line drugs should only be available to such centres.

Various drugs and regimens have been recommended for treating patients with MDR-TB[155,180,199], and their close contacts. However, none of the proposed regimens has been tested in randomised clinical trials. Drugs used in the treatment of MDR-TB vary in terms of anti-tuberculosis activity, convenience of administration, potential toxicity, cross-resistance, and costs (see Table 1)[180]. The list of available second line drugs includes thioamides, several aminoglycosides, the fluoroquinolones, and others (cycloserine, PAS, etc). Regimens should be tailored by an expert using three to five drugs the patient has not previously received and to which DST results show no resistance; a single drug must never be added to a failing regimen[180]. A popular drug combination includes cycloserine, PZA, ethionamide and ofloxacin, plus an injectable agent (kanaycin or capreomycin). Treatment must be given daily and under direct supervision. Once the patient's sputum has converted to consistently negative microscopy, the weaker or more toxic drug can be withdrawn. Treatment should then be continued for 18 additional months[151,180].

Although priority should be given to preventing the emergence of MDR by appropriate treatment of all new TB cases, a second line of containment is the isolation of patients to diminish the spread of the disease[5,81]. Isolation of any TB patient in congregate settings is recommended[127,128], especially in hospitals with immunologically vulnerable patients[128]. Healthcare workers are at risk of infection and deserve appropriate protection. The wisdom of this control strategy is particularly relevant to the management of patients whose therapy has failed or who have documented MDR-TB. The heightened suspicion of TB by physicians and the rigorous application of isolation policies by hospital epidemiologists have been important components of the improving situation in New York.

In deciding how best to control TB, policy makers and responsible clinicians should keep in mind that the cheapest MDR-TB treatment regimen is 100 times more expensive than the best first line regimen[180]. Difficult choices must be made. On balance, the best approach is to focus on curing the largest number of patients and on the prevention of MDR by adhering to standardised SCC regimens[28]. In most settings, DST is more important as a surveillance tool than for individual case management. Countries that have secured these basic strategies may then decide to devote additional resources to fight MDR-TB. With qualified laboratories and available second line drugs, DST has been recommended for all new cases to help tailor the best possible therapeutic regimens under expert supervision[151,200]. In some cases, contact evaluation and chemoprophylaxis may be pursued, although the cost-effectiveness of implementing these recommendations is likely to be marginal.

Since a good standardised four-drug regimen is currently the best way to control

TB and the emergence of MDR, that treatment should be offered to every patient regardless of their socioeconomic status or place of birth. While MDR-TB is more frequent in certain subgroups[8,136], the problem is relatively infrequent and at the same time can occur in anybody. Recommendations could become unnecessarily complex if tailored to each individual patient by remote policy makers. As noted by Comstock, "simplicity is likely to be the key to success"[201]. All new patients should be started on four drugs and all retreatment cases should receive five anti-tuberculosis drugs. Standardised regimens of proven effectiveness are useful not only for countries with a high incidence of TB, but also for those in which the disease is so rare that physicians lack experience[140].

Thus, regardless of the socioeconomic profile of TB patients, uniform regimens should be implemented as recommended[28], with expert consultants deciding on any exceptions. This also applies to people migrating from areas with high MDR-TB levels to those with less. In such settings, access to culturally-sensitive healthcare services is a better approach to MDR-TB control[78] than trying to concoct anti-tuberculosis regimens according to the patient's country of origin. Curing active TB cases is the best way to prevent the spread of the disease, and *M. tuberculosis* is oblivious to borders and socioeconomic or demographic status. As noted in the recently released WHO Guidelines for the Management of Drug-resistant Tuberculosis, "Whatever the situation, the priority decision is to standardise the treatment regimen applied to all new cases of tuberculosis"[180].

4.8.5 Implications of the prevalence of MDR-TB for the number of anti-tuberculosis drugs in standard initial regimens

The response to MDR-TB should not be the establishment or expansion of laboratories able to culture and test for drug susceptibility. Similarly, the levels of MDR-TB do not necessarily call for a revision of standardised anti-tuberculosis treatment. When implemented within a solid TB programme, classic control principles remain valid even in an era of HIV and MDR-TB. For example, in a country with a high prevalence of primary MDR (5%), 95% of the patients on four-drug SCC could still be cured. Changing the number of drugs in standardised regimens for new TB patients in general was not needed in New York, Texas or Korea to curb high rates of drug resistance successfully[86,149,152]. Six-drug regimens were indicated in very few instances.

Currently recommended retreatment regimens initially include five drugs[28]. This number is deemed necessary given the higher prevalence of drug resistance in previously treated patients. From the Global Project we have learned that, while the prevalence of acquired MDR-TB varies widely, the median value is 13%. Likewise, the median prevalence of primary MDR-TB has been estimated at 1.4% for the countries and regions surveyed. Thus the current global recommendation to use a four-drug regimen in new patients would seem appropriate[58]. This is questionable, however, where the prevalence of primary MDR-TB approaches the median acquired MDR level. Where MDR rates exceed, say, 10%, would it be appropriate to increase to five drugs the standardised regimen of new patients? The answer is no, because primary resistance is not the same as acquired drug resistance.

There are several arguments to justify the use of five drugs in retreatment regimens and only four in treating new patients even when the prevalence of primary MDR-TB is high. First, previously treated TB patients not only have MDR more frequently than new patients[190,193], but the degree of resistance of patients with otherwise similar patterns of

drug resistance is much higher (i.e. higher MIC, especially for INH)[15]. Furthermore, the drug-resistant strains harboured by previously treated patients are usually resistant to a larger number of drugs than those in new patients[190,193]. Based on the Global Project estimates, 65% of patients with primary resistance are resistant to a single drug, compared to only 26% of cases with acquired resistance; the median proportion of patients with resistance to three or more drugs is 0.8% and 10%, respectively.

More importantly, primary rates of MDR-TB higher than 10% occur only where there is therapeutic anarchy[60]. A recommendation of five drugs, or more for that matter, to treat all new TB patients is unlikely to be heeded when adherence to the recommended four-drug regimen has obviously not occurred. However, the approach would increase the risk of toxicity and non-compliance. The only certain outcome of introducing a fifth drug (e.g. a quinolone) in such settings would be the development of additional resistance[202] reducing the chances of successful retreatment after initial failure or relapse.

Thus, the answer to a high prevalence of primary MDR-TB is not the provision of second line drugs for the treatment of all new patients. Instead, the tuberculosis control programme should be reorganised to implement the internationally recommended strategies with proven success[28,85,86,149]. A more pertinent question is whether to reduce to three drugs the standardised four-drug SCC initial treatment regimen in areas where rates of drug resistance are low. In the United States, CDC recommends such an approach in communities with less than 4% resistance to INH and declining rates of TB. Although reasonable when levels of primary RMP resistance rates are also under 1%, this policy decision should be tempered by the low marginal cost of the fourth drug in the initial phase of treatment and the extra assurance it provides against the selection of MDR-TB in the long run. A three-drug regimen may have contributed to the situation in the Ivory Coast, where MDR is present in 5.3% of new TB cases despite standardised SCC (with INH, RMP and PZA in the initial regimen for the last 12 years). Regardless of the levels of primary MDR-TB, previously treated patients will still have a higher prevalence and degree of drug resistance and standardised retreatment regimens should include five drugs[28].

One message emerging from this survey is the need for new anti-tuberculosis agents to be developed and tested. This is necessary, not so much to treat MDR-TB (although new drugs would clearly be useful in this role) but to improve the delivery and acceptance of curative treatment: much shorter courses, administered intermittently at longer intervals (i.e. weekly), with no side effects and no cross-resistance with existing drugs. Such products would reduce the likelihood of the various forms of maladministration of anti-TB treatment that are the cause of resistance. Unfortunately, they are still far from being available in routine clinical and public health practice. The same applies to effective vaccines for the prevention of TB that some day will replace BCG. Whatever new drugs are developed, this survey, and our experience with the development of drug resistance, should make it clear that such drugs will only continue to be useful when they are used in the context of a well administered, carefully designed TB control programme.

In conclusion, the prevalence of primary MDR-TB is a good summary indicator of the performance of an NTP. The limitations of such a parameter have been discussed, as well as the potential utility of the Acquired MDR Index. High levels of MDR-TB should not prompt a shift to five-drug regimens for the initial treatment of all new TB patients; resistance to three or four first line drugs is extremely rare. Instead, accurately measured high MDR-TB levels should call for an overhaul of the obviously ineffective control programme that generated the problem. In countries with a high incidence of TB, DST is

more useful as a surveillance tool than as a guide to an individual patient's treatment. Where affordable, retreatment failures and patients with documented MDR-TB should be referred to a specialised centre. Second line anti-tuberculosis drugs should only be dispensed by qualified experts. Additional studies are needed to clarify the transmissibility, trends and clinical impact of MDR-TB. On balance, the WHO/IUATLD-recommended strategy with emphasis on supervised four drug SCC will save more lives and control all forms of TB better than unproved and often unaffordable schemes focusing on the current victims of MDR-TB.

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ANNEX 1

DATA COLLECTION FORMS

1a CLUSTER SAMPLING

Cluster selection

Example: A sample size of 360 tuberculosis patients has been calculated after taking into account the effect of cluster sampling. 30 clusters of 360/30 = 12 patients will have to be selected. The following steps should be taken:

a) establish the list of the diagnostic centres with their annual number of patients (see table below).

b) calculate the cumulative numbers of patients and record them in an additional column. Cumulative number for the second centre will be (number in the first centre) + (number in the second centre). Cumulative number for the third centre will be (cumulative number for the second centre) + (number in the third centre) and so on. The total number of patients diagnosed in the country is 6,322.

c) determine the sampling interval: 6,322 / 30 = **211**

d) select a number between 0 and 211 at random (with a table of random numbers or by using the last digits of a currency note for example). In this case the number selected is **120**.

e) the first cluster is selected using this number **120**: it will be in the first centre because 120 falls between 0 and 246 (number of patients in the first centre).

f) selection of next clusters is performed by adding the sampling interval 211 each time to this first number 120. The next number (120 + 211) = **331** falls between 246 and 1,823 (cumulative number of patients for the second centre), therefore the 2nd cluster is selected in the 2nd centre. The 3rd number (331 + 211) = **542** falls also between 246 and 1,823, the 3rd cluster is therefore selected in the 3rd centre as well.

Name of diagnostic centre	Number of patients diagnosed per year	Cumulative number of patients	Cluster number
A	246	246	1
B	1,577	1,823	2,3,4,5,6,7,8,
C	468	2,291	9
D	340	2,631	10,11
E	220	2,851	12
F	246	3,097	13
G	190	3,287	14,15
H	1,124	4,411	16
I	61	4,472	17,18,19,20,2
J	154	4,626	1
K	139	4,765	
K	60	4,825	22
M	14	4,839	23
N	38	4,877	
O	19	4,896	
P	41	4,937	
Q	120	5,057	
R	455	5,512	
S	51	5,563	24
T	26	5,589	25,26
U	199	5,788	
V	21	5,809	
W	32	5,841	27
X	69	5,910	
Y	6	5,916	28
Z	145	6,061	
AA	129	6,190	
BB	87	6,277	29
CC	10	6,287	
DD	35	6,322	30

Confidence interval calculation

If cluster selection is performed with probability proportional to size (method described above) and if clusters are of the same size, a simplified formula for the confidence interval (CI) around the drug resistance prevalence is:

$$CI = \pm 1.96 \sqrt{\frac{\sum_i (P_i - P)^2}{n(n-1)}}$$

where P is the prevalence calculated for the total sample,
Pi is the prevalence calculated in each cluster i
n is the number of clusters (30)

To calculate the sum of the $(P_i-P)^2$ over all 30 clusters the following table can be used:

Cluster number	P_i	$P_i - P$	$(P_i - P)^2$
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			

The total of the last column can then be used in the formula.

Source: ten Dam H.G. Surveillance of tuberculosis by means of tuberculin surveys. WHO/TB/85.145

1b SAFE SHIPMENT OF INFECTIOUS MATERIAL

For international quality control of susceptibility testing, cultures should be exchanged between the National Reference laboratories and the Supranational Reference Laboratories. Cultures of *M. tuberculosis* are enriched infectious material containing large numbers of viable organisms that can cause disease in humans. The hazard is compounded when cultures of resistant strains are transported.

Some international organisations, such as the Universal Postal Union, the International Civil Aviation Organisation and the International Air Transport Organisation, have developed guidelines and procedures designed to facilitate the safe and expeditious shipment of infectious substances while at the same time ensuring the safety of transport personnel and the general public[1]. These organisations have also developed agreed common definitions, and packaging and labelling requirements[2,3]. Information on the documentation requirements should be obtained from the appropriate national authorities of the country where the cultures are sent.

Infectious substances and diagnostic specimens likely to contain infectious substances require triple packaging in accordance with the recommendations of the United Nations[3]. Cultures of mycobacteria should be shipped on solid medium in screwcap tubes or freeze dried in vials as primary watertight containers. Petri dish cultures and cultures in liquid medium must not be shipped. The primary container should be entirely surrounded by at least two cm of absorbant material and enclosed in a second, durable watertight container. The tissue paper or cellulose wadding in the secondary container must be sufficient to absorb all of the fluid in the specimen in case of leakage of the primary container. Several primary containers may be enclosed in a single secondary container, if the total volume of all the primary containers does not exceed 50 ml and there is no contact between them[4]. Each set of primary and secondary containers should be enclosed in an outer shipping container made of corrugated fibre board, cardboard, wood or other material of equivalent strength.

One copy of the request forms, letters and other information that identifies or describes the specimen should be taped to the outside of the secondary container. Another copy should be sent by air mail to the receiving laboratory and a third retained by the sender. The outer container must bear the infectious substance (biohazard) label. The label should be about 10 cm wide and printed in red on a white background. In addition to the sender's and recipient's addresses, the telephone numbers and fax numbers if available should also be put on the outside of the package.

Compliance with the shipment requirements is the responsibility of the shipper, who must be familiar with the regulations. Failure to comply may result in fines and other penalties. Hand carriage of infectious substances is strictly prohibited by international air carriers, as is the use of diplomatic pouches.

1 *International Air Transport Association. Dangerous Goods Regulations, 37th Edition, effective 1 January 1996, IATA: Montreal - Geneva.*

2 *Safe shipment of specimens and infectious materials. In: World Health Organization. Laboratory biosafety manual. Second edition. Geneva 1993: pp 48-54.*

3 *United Nations. Recommendations on the transport of dangerous goods. Seventh edition revised. New York 1989.*

4 *Kent PT, Kubica GP. Public health mycobacteriology. A guide for the level III laboratory. Atlanta 1985.*

1c FORM 1: SPUTUM SHIPMENT FORM

Country: ..... Diagnostic Centre: .....

Code: ..... Code: .....

IDENTIFICATION OF THE PATIENT

Name: .....

TB district number: ..... Date registered: ☐☐ ☐☐ ☐☐
Day Mo Yr

Sex: ☐ Male ☐ Female

Age: ..... Years

Date of sputum collection: A ..... B .....

Result of smear: .....

1d FORM 2: CLINICAL INFORMATION

Country: ..... Diagnostic Centre: .....

Code: ..... Code: .....

A. IDENTIFICATION OF THE PATIENT

Name: .....

TB district number: ..... Date registered: ☐☐ ☐☐ ☐☐☐☐
Day Mo Yr

Sex: ☐ Male ☐ Female

Age: ..... Years

Date of sputum collection: A ..... B .....

Country specific data (to be decided by the co-ordinating team):

for example, country of origin .....

HIV status ☐

history of drug abuse ☐

B. HISTORY GIVEN BY THE PATIENT

B1 Previously treated for TB? Yes ☐ No ☐

If the answer is no, go to B2, if yes, go to B3.

B2 Standardised history

- how long have you been sick ?.....
- have you had the same symptoms prior to this episode?.....
- have you had other symptoms of lung disease prior to this episode (hemoptysis, chest pain, cough)?.....
- have you had X-ray examinations prior to this episode ?.....
- have you had sputum examinations prior to this episode ? .....
- have you had drug treatment for more than one month ? .....
  if yes, what were the name of the drugs ?.....
- have you ever received injections for more than one month ?.....

Did the patient remember previous treatment for TB after these questions?

Yes ☐ No ☐ If yes continue with B3

B3 Information about previous treatment

- where was the patient treated? .....
- when was the patient treated? .....
- how long was the patient treated?.....
- which drugs were used for treatment?.....
- by whom was the patient treated?.....
- how many courses of treatment were given? .....
- Outcome of the last treatment according to the patient.

cured ☐ not cured ☐ unknown ☐

C. MEDICAL RECORDS

After extensive checking through the medical files and other documents available in the health centre, have you discovered that the patient has been registered for tuberculosis treatment before?

☐ No ☐ Yes

If "Yes", what was the outcome of the last course of chemotherapy:

cured ☐ treatment completed ☐

defaulted ☐ failed ☐

transferred-out ☐

D. FINAL DECISION

D1 Patient has been previously treated for TB for more than a month

Yes ☐ (answer to question B1 or B2 and/or C was 'yes')

No ☐ (answer to B1 and B2 and/orC was 'no')

Doubtful ☐

D2 If yes, what was the outcome of previous treatment ?

cured/treatment completed ☐

failed ☐

defaulted ☐

chronic ☐

relapse/defaulter not distinguishable ☐

unknown ☐

Responsible Officer: .....

1e FORM 3: RESULTS OF BACTERIOLOGICAL EXAMINATION

Country: ..... Diagnostic Centre: .....

Code: ..... Code: .....

A. PATIENT

Number: ..... Date of receipt: ☐☐ ☐☐ ☐☐
Day Mo Yr

B. IDENTIFICATION

Sample A:		Sample B:	
☐	*M. tuberculosis*	☐	*M. tuberculosis*
☐	*M. bovis*	☐	*M. bovis*
☐	*M. africanum*	☐	*M. africanum*
☐	Negative	☐	Negative
☐	Contaminated	☐	Contaminated
☐	Other	☐	Other

C. SUSCEPTIBILITY OF *M. TUBERCULOSIS*

Susceptible to:	Resistant to:
☐ Isoniazid	☐ Isoniazid
☐ Rifampicin	☐ Rifampicin
☐ Ethambutol	☐ Ethambutol
☐ Streptomycin	☐ Streptomycin

Date of receipt: ☐ ☐ ☐
Day Mo Yr

Responsible Officer: .....

This form is to be made out in two copies. The original is to be sent to the diagnostic centre, the copy is filed at the central laboratory.

1f REPORT OF SURVEY RESULTS AND NTP PROFILE

PROFILE FOR ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEILLANCE

COUNTRY .....

1. Total population in year of survey .....

2. Year of Survey_____	Notifications Number	Total	Rate / 100 000
New cases of pulmonary TB	smear +		
	smear -		
New Extrapulmonary TB			
Retreatment cases	smear +		
	smear -		

3. Estimated tuberculosis incidence (all cases)/100000/year.....

4. Estimated proportion of tuberculosis patients HIV+.....

5. Date of establishment of Nationall Tuberculosis Programme .....

6. % of districts covered by NTP.....

7. Are regimens for treatment standardised in the country .....[yes] ..... [no]

8. % of patients detected receiving Short Course Chemotherapy .....

9. Is administration of treatment directly observed?.....[yes] ..... [no]
   If yes, during the first two months? .....[yes] ..... [no]
   If yes, during all the treatment? .....[yes] ..... [no]
   % of patients receiving directly observed treatment.....

10. Date from which directly observed treatment was established as national policy
    .....

11. Are combination drugs used (HR, HRZ) .....[yes] ..... [no]
    If yes, please specify which combination, and.....
    in what percentage of patients? .....

12. Year of introduction of isoniazid in the country's public sector:
    .....

13. Year of introduction of rifampicin in the country's public sector: .....

14. Are TB drugs available in the private market?.....[yes] ..... [no]
    If yes, please specify which drugs and which preparations:
    .....
    .....

15. Estimated % of tuberculosis patients diagnosed and treated in the private sector
    .....
    .....

16. Any study available on quality of drugs in the country?
    .....
    If yes, please specify the results
    .....
    References .....
    .....

DRUG RESISTANCE RESULTS

17. Principal Investigator:

    .....

18. Other members of the WHO/IUATLD Working Group on Global Anti-tuberculosis Drug Resistance Surveillance:

    .....

    .....

19. National Reference Laboratory (NRL)

    .....

20. Supranational Reference Laboratory (SRL)

    .....

21. Concordance between the NRL and SRL:

Absolute numbers	**H**	**R**	**S**	**E**
Resistant strains sent to SRL for QC Resistant strains in agreement				
Sensitive strains sent to SRL for QC Sensitive strains in agreement				

22. How were the strains selected

    .....

23. Survey / Surveillance started

    .....

    Period of enrolment in the survey:

    from .....to.....

24. Sampling method

.....

25. Method for culture

.....

26. Method for susceptibility testing

.....

.....

27. Total number of patients enrolled

.....

28. Age and sex breakdown

	0-14	15-24	25-34	35-44	45-54	55-65	65+
Male							
Female							

PATTERNS OF ANTI-TUBERCULOSIS DRUG RESISTANCE

	Primary			Acquired		
	no		**95% CI**	**no**		**95% CI**
Total tested						
Fully sensitive						
Any resistance						
Mono-resistance						
H						
R						
E						
S						
H+R resistance						
HR						
HRE						
HRS						
HRSE						
H+ other resistance						
HE						
HS						
HES						
R+ other resistance						
RS						
RE						
RES						
Other multi-resistance						
ES						
Any H resistance						
Any R resistance						

Date: ..... Signed by: .....

ANNEX 2

INDIVIDUAL COUNTRY (OR REGION WITHIN COUNTRY) PROFILES

ARGENTINA

YEAR OF SURVEY: **1994**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **34,587,000**
- Tuberculosis case notification:
  *incidence rate: **38.84**/100,000
- Rate ratio people >55 / <15 years old: **20:1**
- Sputum smear positive cases: **5,698**
- Fraction of all pulmonary cases: **55**%
- Case detection rate: **73**%
- Treatment Success: **60**%
- Retreatment Cases: **19**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **8.0**%
- WHO Control Category:
  Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000
- Year N.T.P. was established: **1960**
- Year of Rifampicin Introduction: **1974**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy:
  Full treatment under DOT (<50% of patients)
- Use of Fixed Dose Combination Tablets: **23**%
- Treatment In Private Sector:
  Less than 15% of patients treated in private sector

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Cluster**

Sampling Fraction: **30**%

Study duration: **6** months

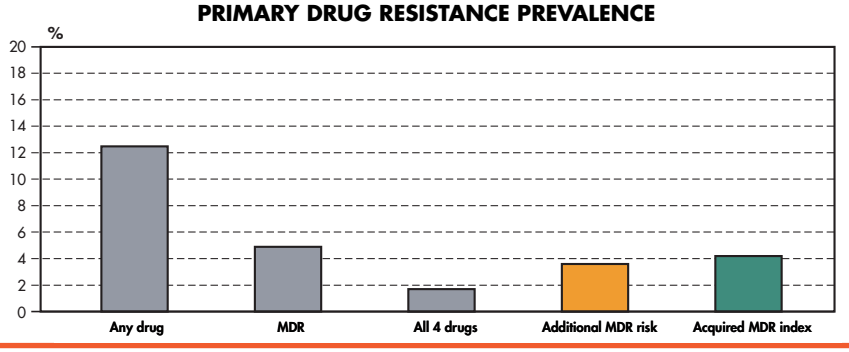
Culture Media: **Loewenstein-Jensen and others**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **99.6**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	606	100	288	100	*	100
SENSITIVE TO ALL 4 DRUGS	**530**	**87.5**	**169**	**58.7**		**82.0**
ANY RESISTANCE	**76**	**12.5**	**119**	**41.3**		**18.0**
Isoniazid (INH)	47	7.8	94	32.6		12.5
Rifampicin (RMP)	31	5.1	77	26.7		9.2
Ethambutol (EMB)	19	3.1	40	13.9		5.2
Streptomycin (SM)	46	7.6	72	25.0		10.9
MONORESISTANCE	**40**	**6.6**	**35**	**12.2**		**7.7**
Isoniazid (INH)	12	2.0	18	6.3		2.8
Rifampicin (RMP)	2	0.3	6	2.1		0.7
Ethambutol (EMB)	1	0.2	1	0.3		0.2
Streptomycin (SM)	25	4.1	10	3.5		4.0
MULTIDRUG RESISTANCE	**28**	**4.6**	**64**	**22.2**		**8.0**
INH + RMP	9	1.5	10	3.5		1.9
INH + RMP + EMB	5	0.8	10	3.5		1.3
INH + RMP + SM	4	0.7	20	6.9		1.9
INH + RMP + EMB + SM	10	1.7	24	8.3		2.9
OTHER PATTERNS	**8**	**1.3**	**20**	**6.9**		**2.4**
INH + EMB	0	0.0	2	0.7		0.1
INH + SM	5	0.8	10	3.5		1.3
INH + EMB + SM	2	0.3	0	0.0		0.3
RMP + EMB	1	0.2	0	0.0		0.1
RMP + SM	0	0.0	5	1.7		0.3
RMP + EMB + SM	0	0.0	2	0.7		0.1
EMB + SM	0	0.0	1	0.3		0.1
NUMBER OF DRUGS RESISTANT TO:						
0	530	87.5	169	58.7		82.0
1	40	6.6	35	12.2		7.7
2	15	2.5	28	9.7		3.9
3	11	1.8	32	11.1		3.6
4	**10**	**1.7**	**24**	**8.3**		**2.9**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

AUSTRALIA

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **18,088,000**
- Tuberculosis case notification:
  *incidence rate: **5.93**/100,000
- Rate ratio people >55 / <15 years old: **41:1**
- Sputum smear positive cases: **(not available)**
- Fraction of all pulmonary cases: **(not available)**
- Case detection rate: **(not available)**
- Treatment Success: **(not available)**
- Retreatment Cases: **9**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **4.0**%
- WHO Control Category:
  Countries not accepting WHO TB control estrategy and TB notification rate <10/100,000
- Year N.T.P. was established: **1950**
- Year of Rifampicin Introduction: **1969**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **96**%
- Use of Directly Observed Therapy:
  Full treatment under DOT (<50% of patients)
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector:
  More than 15% of patients treated in private sector

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

Culture Media: **Loewenstein-Jensen and BACTEC**

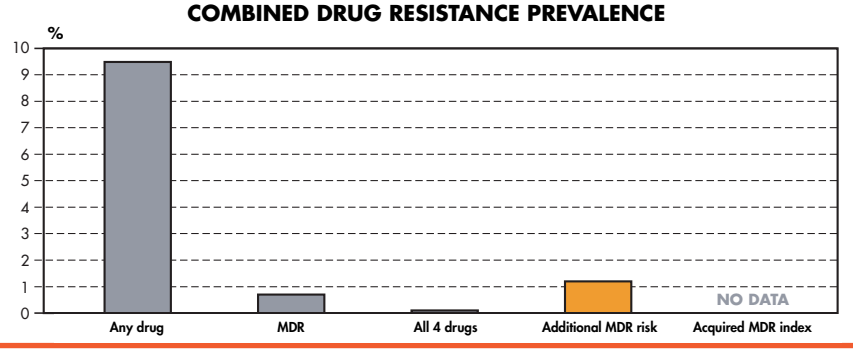
Drug Suceptibility Testing Method: **BACTEC**

Laboratory Accuracy: **100.0**%

Specificity of RMP testing: **100.0**%

* Only combined data reported. Only 191 cases were tested for SM resistance.

COMBINED DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested					705	100
SENSITIVE TO ALL 4 DRUGS					**638**	**90.5**
ANY RESISTANCE					**67**	**9.5**
Isoniazid (INH)					53	7.5
Rifampicin (RMP)					8	1.1
Ethambutol (EMB)					2	0.3
Streptomycin (SM)					53	7.5
MONORESISTANCE					**25**	**3.5**
Isoniazid (INH)					12	1.7
Rifampicin (RMP)					2	0.3
Ethambutol (EMB)					0	0.0
Streptomycin (SM)					11	1.6
MULTIDRUG RESISTANCE					**5**	**0.7**
INH + RMP					0	0.0
INH + RMP + EMB					0	0.0
INH + RMP + SM					4	0.6
INH + RMP + EMB + SM					1	0.1
OTHER PATTERNS					**37**	**5.2**
INH + EMB					0	0.0
INH + SM					35	5.0
INH + EMB + SM					1	0.1
RMP + EMB					0	0.0
RMP + SM					1	0.1
RMP + EMB + SM					0	0.0
EMB + SM					0	0.0
NUMBER OF DRUGS RESISTANT TO:						
0					638	90.5
1					25	3.5
2					36	5.1
3					5	0.7
4					**1**	**0.1**

BENIN

YEAR OF SURVEY: **1995-1997**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **5,409,000**
- Tuberculosis case notification: *incidence rate: **44.37**/100,000
- Rate ratio people >55 / <15 years old: **44:1**
- Sputum smear positive cases: **1,839**
- Fraction of all pulmonary cases: **87**%
- Case detection rate: **56**%
- Treatment Success: **75**%
- Retreatment Cases: **10**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **13.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90% of the population**
- Year N.T.P. was established: **1983**
- Year of Rifampicin Introduction: **1983**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **100**%
- Treatment In Private Sector: **Virtually all patients treated in the pubblic sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **23**%

Study duration: **24** months

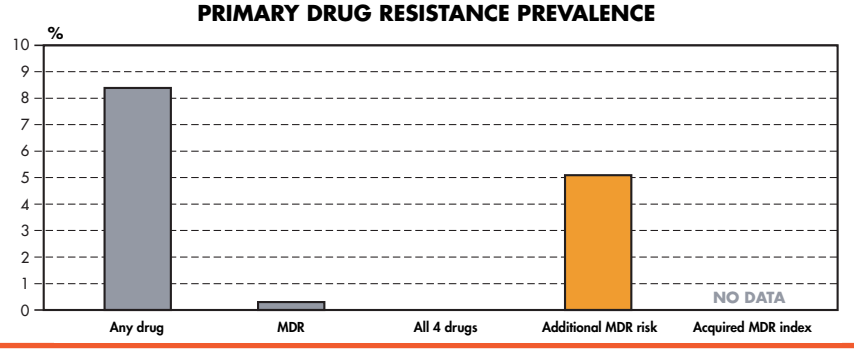
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **87.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	333	100				
SENSITIVE TO ALL 4 DRUGS	**305**	**91.6**				
ANY RESISTANCE	**28**	**8.4**				
Isoniazid (INH)	18	5.4				
Rifampicin (RMP)	1	0.3				
Ethambutol (EMB)	2	0.6				
Streptomycin (SM)	16	4.8				
MONORESISTANCE	**20**	**6.0**				
Isoniazid (INH)	11	3.3				
Rifampicin (RMP)	0	0.0				
Ethambutol (EMB)	0	0.0				
Streptomycin (SM)	9	2.7				
MULTIDRUG RESISTANCE	**1**	**0.3**				
INH + RMP	0	0.0				
INH + RMP + EMB	1	0.3				
INH + RMP + SM	0	0.0				
INH + RMP + EMB + SM	0	0.0				
OTHER PATTERNS	**7**	**2.1**				
INH + EMB	0	0.0				
INH + SM	6	1.8				
INH + EMB + SM	0	0.0				
RMP + EMB	0	0.0				
RMP + SM	0	0.0				
RMP + EMB + SM	0	0.0				
EMB + SM	1	0.3				
NUMBER OF DRUGS RESISTANT TO:						
0	305	91.6				
1	20	6.0				
2	2	2.1				
3	1	0.3				
4	**0**	**0.0**				

BOLIVIA

YEAR OF SURVEY: **1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **7,414,000**
- Tuberculosis case notification: *incidence rate: **129.67**/100,000
- Rate ratio people >55 / <15 years old: **11:1**
- Sputum smear positive cases: **7,010**
- Fraction of all pulmonary cases: **83**%
- Case detection rate: **63**%
- Treatment Success: **64**%
- Retreatment Cases: **25**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **3.1**%
- WHO Control Category: **Countries implementing WHO TB control strategy in 10-90% of the population**
- Year N.T.P. was established: **1956**
- Year of Rifampicin Introduction: **1988**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **65**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **60**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Cluster**

Sampling Fraction: **40**%

Study duration: **11** months

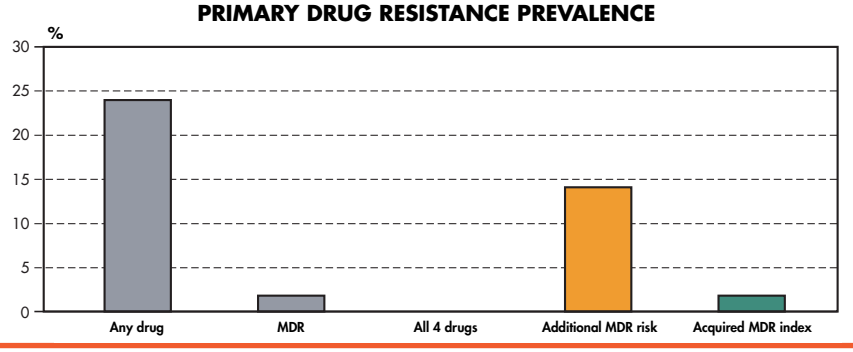
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **91.6**%

Specificity of RMP testing: **98.8**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	498	100	107	100	*	100
SENSITIVE TO ALL 4 DRUGS	**379**	**76.1**	**62**	**57.9**		**71.6**
ANY RESISTANCE	**119**	**23.9**	**45**	**42.1**		**28.4**
Isoniazid (INH)	51	10.2	11	10.3		10.3
Rifampicin (RMP)	30	6.0	20	18.7		9.2
Ethambutol (EMB)	25	5.0	8	7.5		5.6
Streptomycin (SM)	49	9.8	16	15.0		11.1
MONORESISTANCE	**100**	**20.1**	**35**	**32.7**		**23.2**
Isoniazid (INH)	34	6.8	4	3.7		6.1
Rifampicin (RMP)	14	2.8	13	12.1		5.1
Ethambutol (EMB)	18	3.6	5	4.7		3.9
Streptomycin (SM)	34	6.8	13	12.1		8.1
MULTIDRUG RESISTANCE	**6**	**1.2**	**5**	**4.7**		**2.1**
INH + RMP	5	1.0	4	3.7		1.7
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	1	0.2	0	0.0		0.2
INH + RMP + EMB + SM	0	0.0	1	0.9		0.2
OTHER PATTERNS	**21**	**4.2**	**4**	**3.7**		**4.1**
INH + EMB	2	0.4	2	1.9		0.8
INH + SM	9	1.8	0	0.0		1.4
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	5	1.0	0	0.0		0.8
RMP + SM	5	1.0	2	1.9		1.2
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	379	76.1	62	57.9		71.6
1	100	20.1	35	32.7		23.2
2	26	5.2	8	7.5		5.8
3	1	0.2	0	0.0		0.2
4	**0**	**0.0**	**1**	**0.9**		**0.2**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

BOTSWANA

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **1,487,000**
- Tuberculosis case notification: *incidence rate: **380.30**/100,000
- Rate ratio people >55 / <15 years old: **101:1**
- Sputum smear positive cases: **1,903**
- Fraction of all pulmonary cases: **40**%
- Case detection rate: **71**%
- Treatment Success: **72**%
- Retreatment Cases: **10**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **50.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90% of the population**
- Year N.T.P. was established: **1975**
- Year of Rifampicin Introduction: **1986**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Full treatment under DOT (>50% of patients)**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Random**

Sampling Fraction: **10**%

Study duration: **22** months

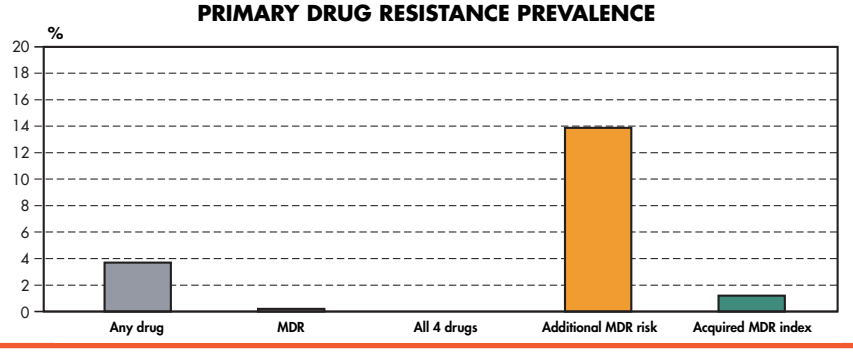
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Resistance ratio method**

Laboratory Accuracy: **95.6**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	407	100	114	100	*	100
SENSITIVE TO ALL 4 DRUGS	**392**	**96.3**	**97**	**85.1**		**95.2**
ANY RESISTANCE	**15**	**3.7**	**17**	**14.9**		**4.8**
Isoniazid (INH)	6	1.5	12	10.5		2.4
Rifampicin (RMP)	4	1.0	9	7.9		1.7
Ethambutol (EMB)	0	0.0	6	5.3		0.5
Streptomycin (SM)	6	1.5	10	8.8		2.2
MONORESISTANCE	**14**	**3.4**	**8**	**7.0**		**3.8**
Isoniazid (INH)	5	1.2	4	3.5		1.5
Rifampicin (RMP)	3	0.7	1	0.9		0.8
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	6	1.5	3	2.6		1.6
MULTIDRUG RESISTANCE	**1**	**0.2**	**7**	**6.1**		**0.8**
INH + RMP	1	0.2	2	1.8		0.4
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	0	0.0	0	0.0		0.0
INH + RMP + EMB + SM	0	0.0	5	4.4		0.4
OTHER PATTERNS	**0**	**0.0**	**2**	**1.8**		**0.2**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	0	0.0	1	0.9		0.1
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	1	0.9		0.1
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	392	96.3	97	85.1		95.2
1	14	3.4	8	7.0		3.8
2	1	0.2	3	2.6		0.5
3	0	0.0	1	0.9		0.1
4	**0**	**0.0**	**5**	**4.4**		**0.4**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

BRAZIL

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **161,790,000**
- Tuberculosis case notification: *incidence rate: **54.46**/100,000
- Rate ratio people >55 / <15 years old: **18:1**
- Sputum smear positive cases: **45,004**
- Fraction of all pulmonary cases: **61**%
- Case detection rate: **77**%
- Treatment Success: **54**%
- Retreatment Cases: **8**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **10.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1964**
- Year of Rifampicin Introduction: **1979**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **100**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Nearly countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **5**%

Study duration: **14** months

Culture Media: **Loewenstein-Jensen**

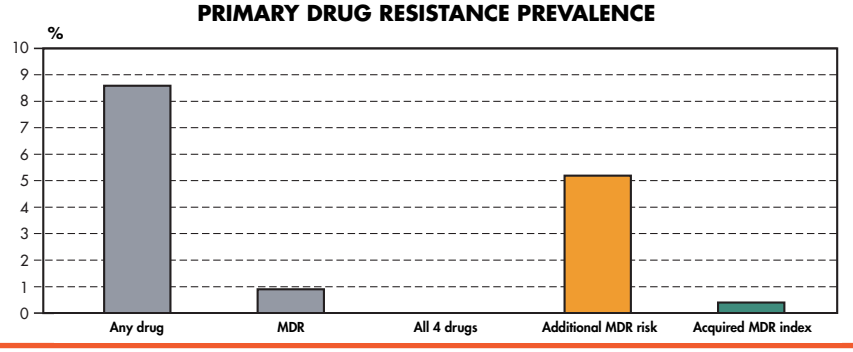
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **96.5**%

Specificity of RMP testing: **100.0**%

* Ongoing survey

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	2095	100	793	100	*	100
SENSITIVE TO ALL 4 DRUGS	**1915**	**91.4**	**679**	**85.6**		**91.0**
ANY RESISTANCE	**180**	**8.6**	**114**	**14.4**		**9.0**
Isoniazid (INH)	124	5.9	89	11.2		6.3
Rifampicin (RMP)	23	1.1	48	6.1		1.5
Ethambutol (EMB)	3	0.1	2	0.3		0.2
Streptomycin (SM)	76	3.6	43	5.4		3.8
MONORESISTANCE	**135**	**6.4**	**58**	**7.3**		**6.5**
Isoniazid (INH)	79	3.8	33	4.2		3.8
Rifampicin (RMP)	4	0.2	5	0.6		0.2
Ethambutol (EMB)	2	0.1	1	0.1		0.1
Streptomycin (SM)	50	2.4	19	2.4		2.4
MULTIDRUG RESISTANCE	**19**	**0.9**	**43**	**5.4**		**1.3**
INH + RMP	18	0.9	31	3.9		1.1
INH + RMP + EMB	0	0.0	1	0.1		0.0
INH + RMP + SM	1	0.0	11	1.4		0.2
INH + RMP + EMB + SM	0	0.0	0	0.0		0.0
OTHER PATTERNS	**26**	**1.2**	**13**	**1.6**		**1.3**
INH + EMB	1	0.0	0	0.0		0.0
INH + SM	25	1.2	13	1.6		1.2
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	1915	91.4	679	85.6		91.0
1	135	6.4	58	7.3		6.5
2	44	2.1	44	5.5		2.4
3	1	0.0	12	1.5		0.2
4	**0**	**0.0**	**0**	**0.0**		**0.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

CHINA (Henan province)

YEAR OF SURVEY: **1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **91,000,000**
- Tuberculosis case notification: *incidence rate: **43**/100,000
- Rate ratio people >55 / <15 years old: **28:1**
- Sputum smear positive cases: **16,803**
- Fraction of all pulmonary cases: **43**%
- Case detection rate: **29**%
- Treatment Success: **91**%
- Retreatment Cases: **30**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in 10-90% of the population**
- Year N.T.P. was established: **1991**
- Year of Rifampicin Introduction: **1972**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **11**%
- Use of Directly Observed Therapy: **Full treatment under DOT (<50% of patients)**
- Use of Fixed Dose Combination Tablets: **20**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Province**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **7**%

Study duration: **9** months

Culture Media: **Loewenstein-Jensen**

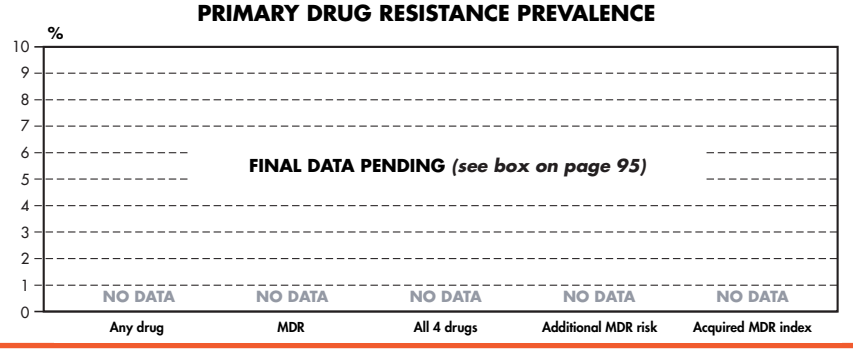
Drug Suceptibility Testing Method: **Absolute concentration method**

Laboratory Accuracy: **89.0**%

Specificity of RMP testing: **88.0**%

* Data undergoing verification at the time of this publication

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested						100
SENSITIVE TO ALL 4 DRUGS						
ANY RESISTANCE						
Isoniazid (INH)						
Rifampicin (RMP)						
Ethambutol (EMB)						
Streptomycin (SM)						
MONORESISTANCE						
Isoniazid (INH)						
Rifampicin (RMP)						
Ethambutol (EMB)						
Streptomycin (SM)						
MULTIDRUG RESISTANCE						
INH + RMP						
INH + RMP + EMB						
INH + RMP + SM						
INH + RMP + EMB + SM						
OTHER PATTERNS						
INH + EMB						
INH + SM						
INH + EMB + SM						
RMP + EMB						
RMP + SM						
RMP + EMB + SM						
EMB + SM						
NUMBER OF DRUGS RESISTANT TO:						
0						
1						
2						
3						
4						

CUBA

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **11,005,866**
- Tuberculosis case notification: *incidence rate: **14.34**/100,000
- Rate ratio people >55 / <15 years old: **164:1**
- Sputum smear positive cases: **835**
- Fraction of all pulmonary cases: **65**%
- Case detection rate: **84**%
- Treatment Success: **91**%
- Retreatment Cases: **7**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **1.3**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90 % of the population**
- Year N.T.P. was established: **1962**
- Year of Rifampicin Introduction: **1982**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Full treatment under DOT (>50% of patients)**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **52**%

Study duration: **12** months

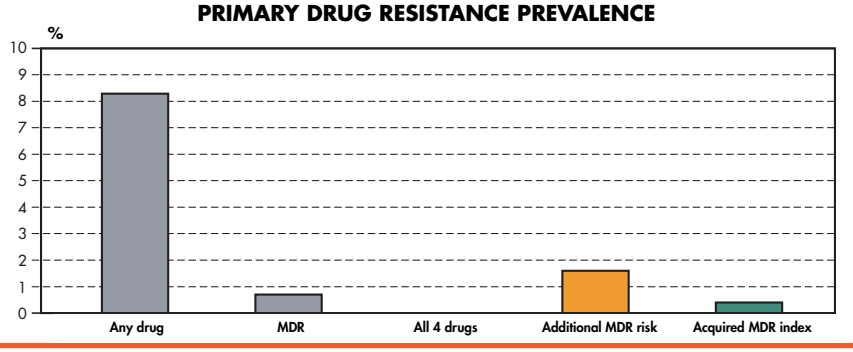
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **84.0**%

Specificity of RMP testing: **80.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	763	100	23	100	786	100
SENSITIVE TO ALL 4 DRUGS	**700**	**91.7**	**2**	**8.7**	**702**	**89.3**
ANY RESISTANCE	**63**	**8.3**	**21**	**91.3**	**84**	**10.7**
Isoniazid (INH)	15	2.0	7	30.4	22	2.8
Rifampicin (RMP)	7	0.9	4	17.4	11	1.4
Ethambutol (EMB)	0	0.0	0	0.0	0	0.0
Streptomycin (SM)	53	6.9	19	82.6	72	9.2
MONORESISTANCE	**55**	**7.2**	**15**	**65.2**	**70**	**8.9**
Isoniazid (INH)	8	1.0	2	8.7	10	1.3
Rifampicin (RMP)	1	0.1	0	0.0	1	0.1
Ethambutol (EMB)	0	0.0	0	0.0	0	0.0
Streptomycin (SM)	46	6.0	13	56.5	59	7.5
MULTIDRUG RESISTANCE	**5**	**0.7**	**3**	**13.0**	**8**	**1.0**
INH + RMP	1	0.1	0	0.0	1	0.1
INH + RMP + EMB	0	0.0	0	0.0	0	0.0
INH + RMP + SM	4	0.5	3	13.0	7	0.9
INH + RMP + EMB + SM	0	0.0	0	0.0	0	0.0
OTHER PATTERNS	**3**	**0.4**	**3**	**13.0**	**6**	**0.8**
INH + EMB	0	0.0	0	0.0	0	0.0
INH + SM	2	0.3	2	8.7	4	0.5
INH + EMB + SM	0	0.0	0	0.0	0	0.0
RMP + EMB	0	0.0	0	0.0	0	0.0
RMP + SM	1	0.1	1	4.3	2	0.3
RMP + EMB + SM	0	0.0	0	0.0	0	0.0
EMB + SM	0	0.0	0	0.0	0	0.0
NUMBER OF DRUGS RESISTANT TO:						
0	700	91.7	2	8.7	702	89.3
1	55	7.2	15	65.2	70	8.9
2	4	0.5	3	13.0	7	0.9
3	4	0.5	3	13.0	7	0.9
4	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**

CZECH REPUBLIC

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **10,296,000**
- Tuberculosis case notification: *incidence rate: **17.81**/100,000
- Rate ratio people >55 / <15 years old: **111:1**
- Sputum smear positive cases: **487**
- Fraction of all pulmonary cases: **32**%
- Case detection rate: **42**%
- Treatment Success: **73**%
- Retreatment Cases: **3**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0** %
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90 % of the population**
- Year N.T.P. was established: **1982**
- Year of Rifampicin Introduction: **1980**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **75**%
- Use of Directly Observed Therapy: **Full treatment under DOT (>50% of patients)**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **6** months

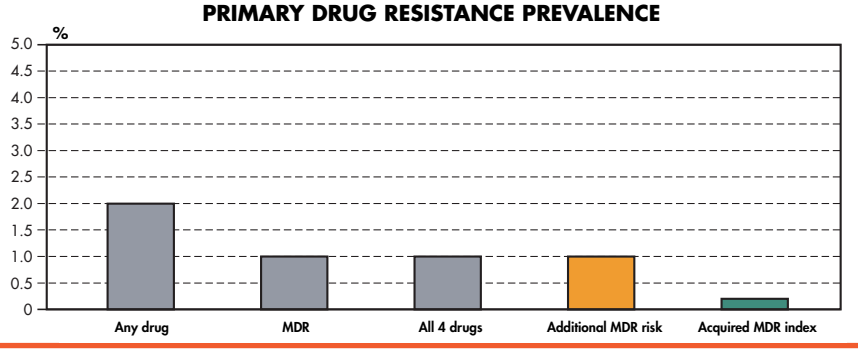
Culture Media: **Loewenstein-Jensen and others**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **89.4**%

Specificity of RMP testing: **87.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
number of strains tested	199	100	16	100	*	100
SENSITIVE TO ALL 4 DRUGS	**195**	**98.0**	**14**	**87.5**		**97.7**
ANY RESISTANCE	**4**	**2.0**	**2**	**12.5**		**2.3**
Isoniazid (INH)	4	2.0	2	12.5		2.3
Rifampicin (RMP)	2	1.0	1	6.3		1.2
Ethambutol (EMB)	2	1.0	1	6.3		1.2
Streptomycin (SM)	2	1.0	1	6.3		1.2
MONORESISTANCE	**2**	**1.0**	**1**	**6.3**		**1.2**
Isoniazid (INH)	2	1.0	1	6.3		1.2
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	0	0.0	0	0.0		0.0
MULTIDRUG RESISTANCE	**2**	**1.0**	**1**	**6.3**		**1.2**
INH + RMP	0	0.0	0	0.0		0.0
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	0	0.0	0	0.0		0.0
INH + RMP + EMB + SM	2	1.0	1	6.3		1.2
OTHER PATTERNS	**0**	**0.0**	**0**	**0.0**		**0.0**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	0	0.0	0	0.0		0.0
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	195	98.0	14	87.5		97.7
1	2	1.0	1	6.3		1.2
2	0	0.0	0	0.0		0.0
3	0	0.0	0	0.0		0.0
4	**2**	**1.0**	**1**	**6.3**		**1.2**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

DOMINICAN REPUBLIC

YEAR OF SURVEY: **1994-1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **7,823,000**
- Tuberculosis case notification: *incidence rate: **51.81**/100,000
- Rate ratio people >55 / <15 years old: **42:1**
- Sputum smear positive cases: **2,187**
- Fraction of all pulmonary cases: **61**%
- Case detection rate: **56**%
- Treatment Success: **71**%
- Retreatment Cases: **16**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **10.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1985**
- Year of Rifampicin Introduction: **1979**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **60**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **85**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **20**%

Study duration: **21** months

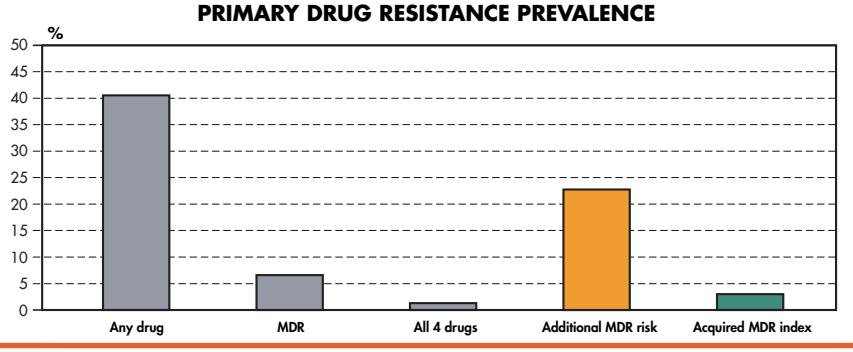
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **94.4**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	303	100	117	100	*	100
SENSITIVE TO ALL 4 DRUGS	**180**	**59.4**	**56**	**47.9**		**57.6**
ANY RESISTANCE	**123**	**40.6**	**61**	**52.1**		**42.4**
Isoniazid (INH)	60	19.8	43	36.8		22.4
Rifampicin (RMP)	49	16.2	37	31.6		18.6
Ethambutol (EMB)	11	3.6	15	12.8		5.1
Streptomycin (SM)	64	21.1	30	25.6		21.8
MONORESISTANCE	**78**	**25.7**	**26**	**22.2**		**25.2**
Isoniazid (INH)	26	8.6	12	10.3		8.8
Rifampicin (RMP)	21	6.9	10	8.5		7.2
Ethambutol (EMB)	1	0.3	0	0.0		0.3
Streptomycin (SM)	30	9.9	4	3.4		8.9
MULTIDRUG RESISTANCE	**20**	**6.6**	**23**	**19.7**		**8.6**
INH + RMP	9	3.0	3	2.6		2.9
INH + RMP + EMB	1	0.3	3	2.6		0.7
INH + RMP + SM	6	2.0	10	8.5		3.0
INH + RMP + EMB + SM	4	1.3	7	6.0		2.0
OTHER PATTERNS	**25**	**8.3**	**12**	**10.3**		**8.6**
INH + EMB	0	0.0	2	1.7		0.3
INH + SM	13	4.3	4	3.4		4.2
INH + EMB + SM	1	0.3	2	1.7		0.5
RMP + EMB	1	0.3	1	0.9		0.4
RMP + SM	7	2.3	3	2.6		2.3
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	3	1.0	0	0.0		0.8
NUMBER OF DRUGS RESISTANT TO:						
0	180	59.4	56	47.9		57.6
1	78	25.7	26	22.2		25.2
2	33	10.9	13	11.1		10.9
3	8	2.6	15	12.8		4.2
4	**4**	**1.3**	**7**	**6.0**		**2.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

ENGLAND & WALES

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **51,506,127**
- Tuberculosis case notification: *incidence rate: **10.6**/100,000
- Rate ratio people >55 / <15 years old: **62:1**
- Sputum smear positive cases: **(not available)**
- Fraction of all pulmonary cases: **(not available)**
- Case detection rate: **(not available)**
- Treatment Success: **65**%
- Retreatment Cases: **9**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **3.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **No NTP**
- Year of Rifampicin Introduction: **1969**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **67**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

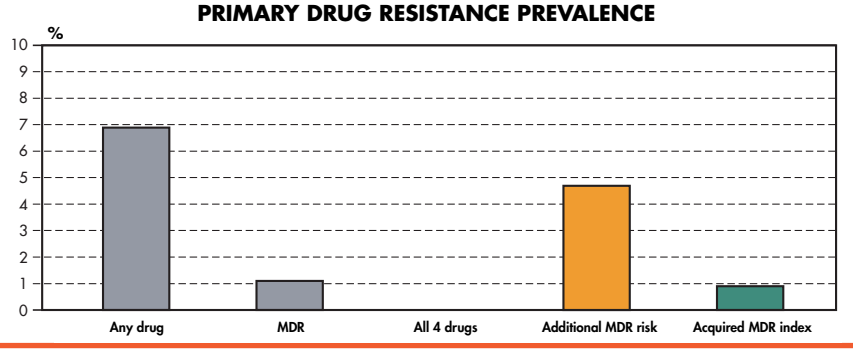
Culture Media: **Loewenstein-Jensen and BACTEC**

Drug Suceptibility Testing Method: **Resistance ratio method**

Laboratory Accuracy: **99.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	2742	100	148	100	2,890	100
SENSITIVE TO ALL 4 DRUGS	**2553**	**93.1**	**100**	**67.6**	**2,653**	**91.8**
ANY RESISTANCE	**189**	**6.9**	**48**	**32.4**	**237**	**8.2**
Isoniazid (INH)	152	5.5	44	29.7	196	6.8
Rifampicin (RMP)	34	1.2	26	17.6	60	2.1
Ethambutol (EMB)	7	0.3	6	4.1	13	0.4
Streptomycin (SM)	69	2.5	14	9.5	83	2.9
MONORESISTANCE	**126**	**4.6**	**18**	**12.2**	**144**	**5.0**
Isoniazid (INH)	90	3.3	14	9.5	104	3.6
Rifampicin (RMP)	5	0.2	1	0.7	6	0.2
Ethambutol (EMB)	1	0.0	0	0.0	1	0.0
Streptomycin (SM)	30	1.1	3	2.0	33	1.1
MULTIDRUG RESISTANCE	**29**	**1.1**	**25**	**16.9**	**54**	**1.9**
INH + RMP	20	0.7	15	10.1	35	1.2
INH + RMP + EMB	3	0.1	3	2.0	6	0.2
INH + RMP + SM	5	0.2	5	3.4	10	0.3
INH + RMP + EMB + SM	1	0.0	2	1.4	3	0.1
OTHER PATTERNS	**33**	**1.2**	**5**	**3.4**	**38**	**1.3**
INH + EMB	0	0.0	1	0.7	1	0.0
INH + SM	31	1.1	4	2.7	35	1.2
INH + EMB + SM	2	0.1	0	0.0	2	0.1
RMP + EMB	0	0.0	0	0.0	0	0.0
RMP + SM	0	0.0	0	0.0	0	0.0
RMP + EMB + SM	0	0.0	0	0.0	0	0.0
EMB + SM	0	0.0	0	0.0	0	0.0
NUMBER OF DRUGS RESISTANT TO:						
0	2553	93.1	100	67.6	2,653	91.8
1	126	4.6	18	12.2	144	5.0
2	51	1.9	20	13.5	71	2.5
3	10	0.4	8	5.4	18	0.6
4	**1**	**0.0**	**2**	**1.4**	**3**	**0.1**

ESTONIA

YEAR OF SURVEY: **1994**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **1,530,000**
- Tuberculosis case notification: *incidence rate: **40.78**/100,000
- Rate ratio people >55 / <15 years old: **18:1**
- Sputum smear positive cases: **369**
- Fraction of all pulmonary cases: **75**%
- Case detection rate: **89**%
- Treatment Success: **65**%
- Retreatment Cases: **17**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **No NTP**
- Year of Rifampicin Introduction: **1976**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **0**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Nearly countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

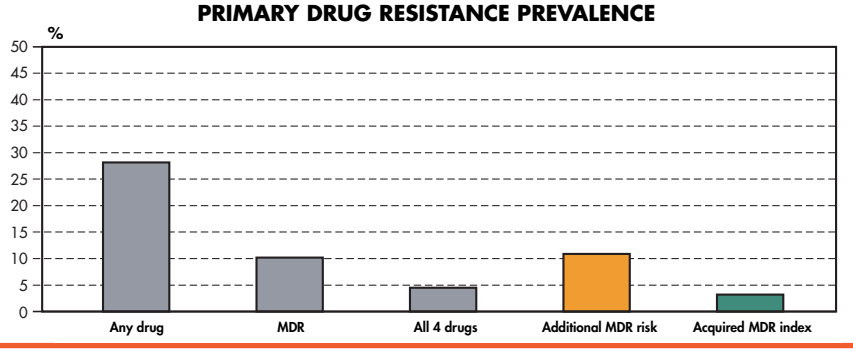
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Various**

Laboratory Accuracy: **97.5**%

Specificity of RMP testing: **93.5**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	266	100	26	100	*	100
SENSITIVE TO ALL 4 DRUGS	**191**	**71.8**	**14**	**53.8**		**68.8**
ANY RESISTANCE	**75**	**28.2**	**12**	**46.2**		**31.2**
Isoniazid (INH)	56	21.1	12	46.2		25.3
Rifampicin (RMP)	27	10.2	5	19.2		11.7
Ethambutol (EMB)	19	7.1	5	19.2		9.2
Streptomycin (SM)	56	21.1	10	38.5		24.0
MONORESISTANCE	**30**	**11.3**	**2**	**7.7**		**10.7**
Isoniazid (INH)	11	4.1	2	7.7		4.7
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	2	0.8	0	0.0		0.6
Streptomycin (SM)	17	6.4	0	0.0		5.3
MULTIDRUG RESISTANCE	**27**	**10.2**	**5**	**19.2**		**11.7**
INH + RMP	6	2.3	0	0.0		1.9
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	9	3.4	2	7.7		4.1
INH + RMP + EMB + SM	12	4.5	3	11.5		5.7
OTHER PATTERNS	**18**	**6.8**	**5**	**19.2**		**8.9**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	13	4.9	3	11.5		6.0
INH + EMB + SM	5	1.9	2	7.7		2.9
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	91	71.8	14	53.8		68.8
1	30	11.3	2	7.7		10.7
2	19	7.1	3	11.5		7.9
3	14	5.3	4	15.4		7.0
4	**12**	**4.5**	**3**	**11.5**		**5.7**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

FRANCE

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **57,981,000**
- Tuberculosis case notification: *incidence rate: **15.04**/100,000
- Rate ratio people >55 / <15 years old: **45:1**
- Sputum smear positive cases: **3449**
- Fraction of all pulmonary cases: **54**%
- Case detection rate: **66**%
- Treatment Success: **65**%
- Retreatment Cases: **10**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **12.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **No NTP**
- Year of Rifampicin Introduction: **1967**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **20**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Sentinel sites**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **24** months

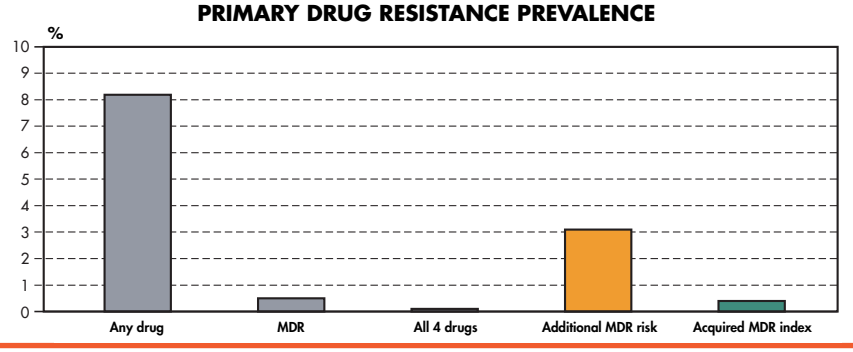
Culture Media: **Loewenstein-Jensen and BACTEC**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **(not yet available)**

Specificity of RMP testing: **(not yet available)**

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
number of strains tested	1491	100	195	100	*	100
SENSITIVE TO ALL 4 DRUGS	**1368**	**91.8**	**153**	**78.5**		**90.4**
ANY RESISTANCE	**123**	**8.2**	**42**	**21.5**		**9.6**
Isoniazid (INH)	51	3.4	27	13.8		4.5
Rifampicin (RMP)	11	0.7	13	6.7		1.3
Ethambutol (EMB)	5	0.3	4	2.1		0.5
Streptomycin (SM)	104	7.0	23	11.8		7.5
MONORESISTANCE	**84**	**5.6**	**24**	**12.3**		**6.3**
Isoniazid (INH)	12	0.8	9	4.6		1.2
Rifampicin (RMP)	3	0.2	5	2.6		0.4
Ethambutol (EMB)	2	0.1	0	0.0		0.1
Streptomycin (SM)	67	4.5	10	5.1		4.6
MULTIDRUG RESISTANCE	**8**	**0.5**	**8**	**4.1**		**0.9**
INH + RMP	2	0.1	5	2.6		0.4
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	5	0.3	0	0.0		0.3
INH + RMP + EMB + SM	1	0.1	3	1.5		0.2
OTHER PATTERNS	**31**	**2.1**	**10**	**5.1**		**2.4**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	29	1.9	9	4.6		2.2
INH + EMB + SM	2	0.1	1	0.5		0.2
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	1368	91.8	153	78.5		90.4
1	84	5.6	24	12.3		6.3
2	31	2.1	14	7.2		2.6
3	7	0.5	1	0.5		0.5
4	**1**	**0.1**	**3**	**1.5**		**0.2**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

INDIA (Delhi state)

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **10,000,000**
- Tuberculosis case notification: *incidence rate: **483.9**/100,000
- Rate ratio people >55 / <15 years old: **15:1**
- Sputum smear positive cases: **11,657**
- Fraction of all pulmonary cases: **27**%
- Case detection rate: **28**%
- Treatment Success: **83**%
- Retreatment Cases: **27**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **1.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in < 10% of the population**
- Year N.T.P. was established: **1962**
- Year of Rifampicin Introduction: **1982**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **40**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **(not available)**
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Province**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **6** months

Culture Media: **Loewenstein-Jensen**

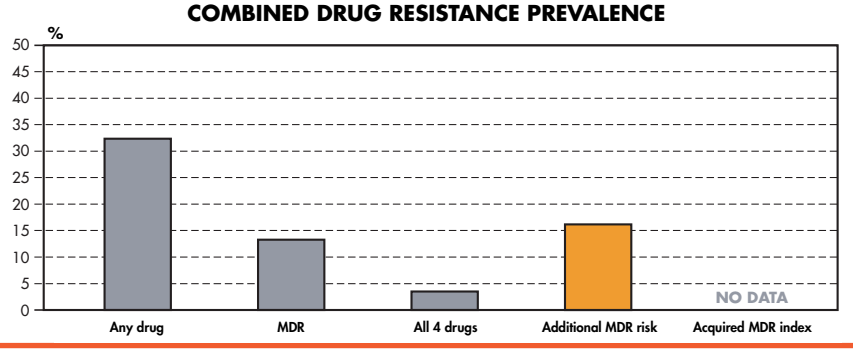
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **90.0**%

Specificity of RMP testing: **100.0**%

* Only combined data reported

COMBINED DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested					2240	100
SENSITIVE TO ALL 4 DRUGS					**1514**	**67.6**
ANY RESISTANCE					**726**	**32.4**
Isoniazid (INH)					646	28.8
Rifampicin (RMP)					314	14.0
Ethambutol (EMB)					156	7.0
Streptomycin (SM)					406	18.1
MONORESISTANCE					**245**	**10.9**
Isoniazid (INH)					181	8.1
Rifampicin (RMP)					7	0.3
Ethambutol (EMB)					4	0.2
Streptomycin (SM)					53	2.4
MULTIDRUG RESISTANCE					**298**	**13.3**
INH + RMP					94	4.2
INH + RMP + EMB					22	1.0
INH + RMP + SM					104	4.6
INH + RMP + EMB + SM					78	3.5
OTHER PATTERNS					**183**	**8.2**
INH + EMB					12	0.5
INH + SM					123	5.5
INH + EMB + SM					32	1.4
RMP + EMB					0	0.0
RMP + SM					8	0.4
RMP + EMB + SM					1	0.0
EMB + SM					7	0.3
NUMBER OF DRUGS RESISTANT TO:						
0					1514	67.6
1					245	10.9
2					244	10.9
3					159	7.1
4					**78**	**3.5**

ITALY

YEAR OF SURVEY: **1994**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **57,187,000**
- Tuberculosis case notification: *incidence rate: **9.84**/100,000
- Rate ratio people >55 / <15 years old: **(not available)**
- Sputum smear positive cases: **1,413**
- Fraction of all pulmonary cases: **34**%
- Case detection rate: **22**%
- Treatment Success: **80**%
- Retreatment Cases: **4**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **8.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate <10/100,000**
- Year N.T.P. was established: **No NTP**
- Year of Rifampicin Introduction: **1968**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **30**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **25**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **HIV population**

Sampling Method: **Cluster**

Sampling Fraction: **32**%

Study duration: **18** months

Culture Media: **Loewenstein-Jensen**

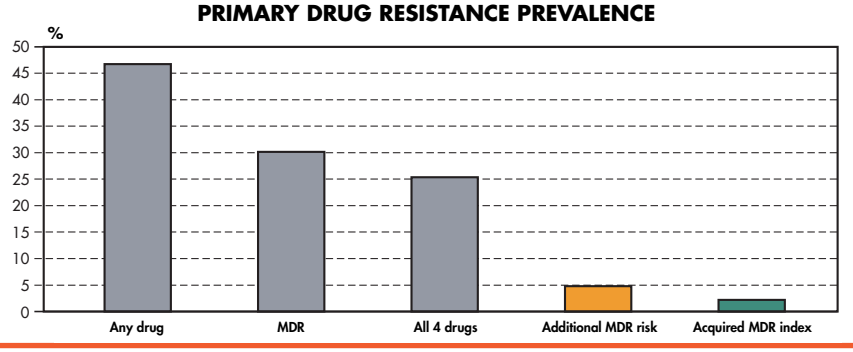
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **97.0**%

Specificity of RMP testing: **100.0**%

* Excluded from global analysis because results were deemed non representative (only HIV-infected patients tested and the survey coincided with a nosocomial outbreak of MDR-TB)

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE*

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	126	100	41	100		
SENSITIVE TO ALL 4 DRUGS	**67**	**53.2**	**15**	**36.6**		
ANY RESISTANCE	**59**	**46.6**	**26**	**63.4**		
Isoniazid (INH)	43	34.1	22	54.0		
Rifampicin (RMP)	39	31.0	23	56.0		
Ethambutol (EMB)	32	25.4	20	49.0		
Streptomycin (SM)	58	46.0	24	59.0		
MONORESISTANCE	**16**	**12.7**	**4**	**9.7**		
Isoniazid (INH)	0	0.0	0	0.0		
Rifampicin (RMP)	1	0.8	1	2.4		
Ethambutol (EMB)	0	0.0	0	0.0		
Streptomycin (SM)	15	11.9	3	7.3		
MULTIDRUG RESISTANCE	**38**	**30.7**	**22**	**53.7**		
INH + RMP	0	0.0	1	2.4		
INH + RMP + EMB	0	0.0	0	0.0		
INH + RMP + SM	6	4.7	1	2.4		
INH + RMP + EMB + SM	32	25.4	20	48.6		
OTHER PATTERNS	**5**	**3.9**	**0**	**0.0**		
INH + EMB	0	0.0	0	0.0		
INH + SM	5	3.9	0	0.0		
INH + EMB + SM	0	0.0	0	0.0		
RMP + EMB	0	0.0	0	0.0		
RMP + SM	0	0.0	0	0.0		
RMP + EMB + SM	0	0.0	0	0.0		
EMB + SM	0	0.0	0	0.0		
NUMBER OF DRUGS RESISTANT TO:						
0	67	53.2	15	36.6		
1	16	12.7	4	9.8		
2	5	3.9	1	2.4		
3	6	4.8	1	2.4		
4	**32**	**25.4**	**20**	**48.8**		

*** Only HIV-positive patients included and survey major nosocomial outbreak of MDR-TB.**

IVORY COAST

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **14,253,000**
- Tuberculosis case notification: *incidence rate: **84.11**/100,000
- Rate ratio people >55 / <15 years old: **7:1**
- Sputum smear positive cases: **8,254**
- Fraction of all pulmonary cases: **85**%
- Case detection rate: **66**%
- Treatment Success: **67**%
- Retreatment Cases: **6**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **45.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90 % of the population**
- Year N.T.P. was established: **1985**
- Year of Rifampicin Introduction: **1985**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **90**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **5**%

Study duration: **12** months

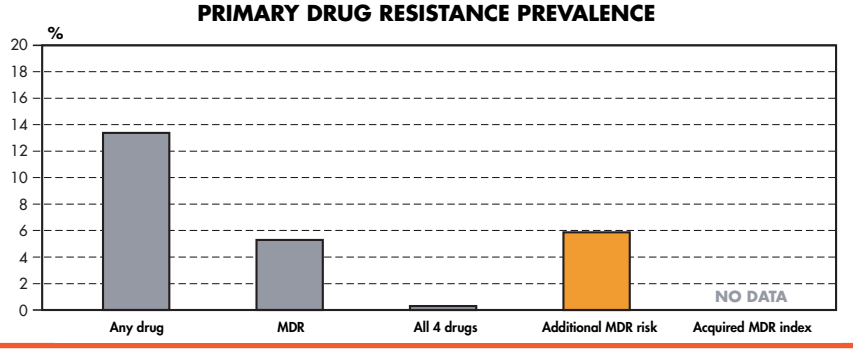
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **93.9**%

Specificity of RMP testing: **98.1**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	320	100				
SENSITIVE TO ALL 4 DRUGS	**277**	**86.6**				
ANY RESISTANCE	**43**	**13.4**				
Isoniazid (INH)	36	11.3				
Rifampicin (RMP)	17	5.3				
Ethambutol (EMB)	1	0.3				
Streptomycin (SM)	22	6.9				
MONORESISTANCE	**17**	**5.3**				
Isoniazid (INH)	10	3.1				
Rifampicin (RMP)	0	0.0				
Ethambutol (EMB)	0	0.0				
Streptomycin (SM)	7	2.2				
MULTIDRUG RESISTANCE	**17**	**5.3**				
INH + RMP	11	3.4				
INH + RMP + EMB	0	0.0				
INH + RMP + SM	5	1.6				
INH + RMP + EMB + SM	1	0.3				
OTHER PATTERNS	**9**	**2.8**				
INH + EMB	0	0.0				
INH + SM	9	2.8				
INH + EMB + SM	0	0.0				
RMP + EMB	0	0.0				
RMP + SM	0	0.0				
RMP + EMB + SM	0	0.0				
EMB + SM	0	0.0				
NUMBER OF DRUGS RESISTANT TO:						
0	277	86.6				
1	17	5.3				
2	20	6.3				
3	5	1.6				
4	**1**	**0.3**				

KENYA

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **28,261,000**
- Tuberculosis case notification: *incidence rate: **99.58**/100,000
- Rate ratio people >55 / <15 years old: **26:1**
- Sputum smear positive cases: **13,934**
- Fraction of all pulmonary cases: **59**%
- Case detection rate: **78**%
- Treatment Success: **73**%
- Retreatment Cases: **20**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **30.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in 10-90% of the population**
- Year N.T.P. was established: **1956**
- Year of Rifampicin Introduction: **1993**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **60**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **50**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Nearly countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **15**%

Study duration: **5** months

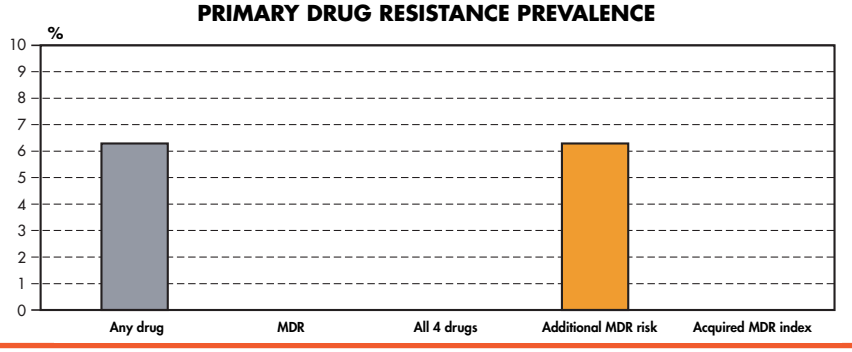
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Resistance ratio method**

Laboratory Accuracy: **97.4**%

Specificity of RMP testing: **99.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	445	100	46	100	*	100
SENSITIVE TO ALL 4 DRUGS	**417**	**93.7**	**29**	**63.0**		**87.6**
ANY RESISTANCE	**28**	**6.3**	**17**	**37.0**		**12.4**
Isoniazid (INH)	28	6.3	17	37.0		12.4
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	4	0.9	3	6.5		2.0
MONORESISTANCE	**24**	**5.4**	**14**	**30.4**		**10.4**
Isoniazid (INH)	24	5.4	14	30.4		10.4
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	0	0.0	0	0.0		0.0
MULTIDRUG RESISTANCE	**0**	**0.0**	**0**	**0.0**		**0.0**
INH + RMP	0	0.0	0	0.0		0.0
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	0	0.0	0	0.0		0.0
INH + RMP + EMB + SM	0	0.0	0	0.0		0.0
OTHER PATTERNS	**4**	**0.9**	**3**	**6.5**		**2.0**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	4	0.9	3	6.5		2.0
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	417	93.7	29	63.0		87.6
1	24	5.4	14	30.4		10.4
2	4	0.9	3	6.5		2.0
3	0	0.0	0	0.0		0.0
4	**0**	**0.0**	**0**	**0.0**		**0.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

LATVIA

YEAR OF SURVEY: **1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **2,557,000**
- Tuberculosis case notification: *incidence rate: **60.27**/100,000
- Rate ratio people >55 / <15 years old: **3:1**
- Sputum smear positive cases: **504**
- Fraction of all pulmonary cases: **42**%
- Case detection rate: **63**%
- Treatment Success: **55**%
- Retreatment Cases: **19**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1960**
- Year of Rifampicin Introduction: **1970**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **70**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **5**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **6** months

Culture Media: **Loewenstein-Jensen**

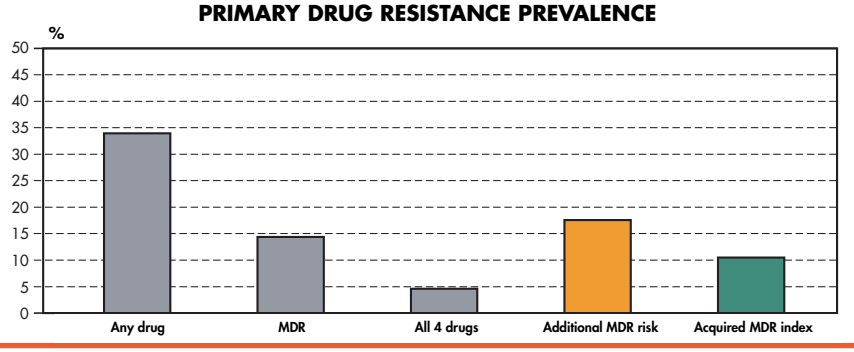
Drug Suceptibility Testing Method: **Various**

Laboratory Accuracy: **93.8**%

Specificity of RMP testing: **86.0**%

* Ongoing survey

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	347	100	228	100	*	100
SENSITIVE TO ALL 4 DRUGS	**229**	**66.0**	**60**	**26.3**		**58.4**
ANY RESISTANCE	**118**	**34.0**	**168**	**73.7**		**41.6**
Isoniazid (INH)	110	31.7	159	69.7		39.0
Rifampicin (RMP)	51	14.7	132	57.9		23.0
Ethambutol (EMB)	17	4.9	41	18.0		7.4
Streptomycin (SM)	97	28.0	148	64.9		35.1
MONORESISTANCE	**26**	**7.5**	**11**	**4.8**		**7.0**
Isoniazid (INH)	19	5.5	6	2.6		4.9
Rifampicin (RMP)	0	0.0	4	1.8		0.3
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	7	2.0	1	0.4		1.7
MULTIDRUG RESISTANCE	**50**	**14.4**	**124**	**54.4**		**22.1**
INH + RMP	2	0.6	10	4.4		1.3
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	32	9.2	75	32.9		13.8
INH + RMP + EMB + SM	16	4.6	39	17.1		7.0
OTHER PATTERNS	**42**	**12.1**	**33**	**14.5**		**12.6**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	40	11.5	27	11.8		11.6
INH + EMB + SM	1	0.3	2	0.9		0.4
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	1	0.3	4	1.8		0.6
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	229	66.0	60	26.3		58.4
1	26	7.5	11	4.8		7.0
2	43	12.4	41	18.0		13.5
3	33	9.5	77	33.8		14.2
4	**16**	**4.6**	**39**	**17.1**		**7.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

LESOTHO

YEAR OF SURVEY: **1994-1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **2,050,000**
- Tuberculosis case notification: *incidence rate: **236.39**/100,000
- Rate ratio people >55 / <15 years old: **46:1**
- Sputum smear positive cases: **1361**
- Fraction of all pulmonary cases: **34**%
- Case detection rate: **59**%
- Treatment Success: **56**%
- Retreatment Cases: **6**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **27.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90% of the population**
- Year N.T.P. was established: **1986**
- Year of Rifampicin Introduction: **1980**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **100**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **35**%

Study duration: **18** months

Culture Media: **Loewenstein-Jensen**

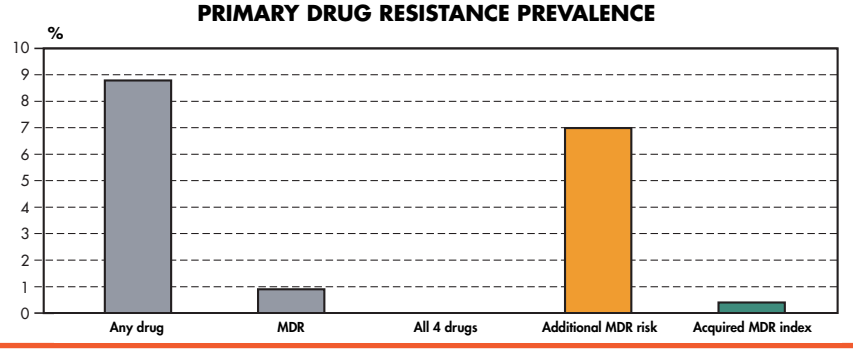
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **94.0**%

Specificity of RMP testing: **100.0**%

* Children under 15 years of age not reported

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	330	100	53	100	*	100
SENSITIVE TO ALL 4 DRUGS	**301**	**91.2**	**35**	**66.0**		**89.6**
ANY RESISTANCE	**29**	**8.8**	**18**	**34.0**		**10.4**
Isoniazid (INH)	26	7.9	16	30.2		9.3
Rifampicin (RMP)	3	0.9	3	5.7		1.2
Ethambutol (EMB)	0	0.0	2	3.8		0.2
Streptomycin (SM)	10	3.0	9	17.0		3.9
MONORESISTANCE	**20**	**6.1**	**11**	**20.8**		**7.0**
Isoniazid (INH)	17	5.2	9	17.0		5.9
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	3	0.9	2	3.8		1.1
MULTIDRUG RESISTANCE	**3**	**0.9**	**3**	**5.7**		**1.2**
INH + RMP	2	0.6	0	0.0		0.6
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	1	0.3	2	3.8		0.5
INH + RMP + EMB + SM	0	0.0	1	1.9		0.1
OTHER PATTERNS	**6**	**1.8**	**4**	**7.5**		**2.2**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	6	1.8	3	5.7		2.1
INH + EMB + SM	0	0.0	1	1.9		0.1
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	301	91.2	35	66.0		89.6
1	20	6.1	11	20.8		7.0
2	8	2.4	3	5.7		2.6
3	1	0.3	3	5.7		0.6
4	**0**	**0.0**	**1**	**1.9**		**0.1**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

NEPAL

YEAR OF SURVEY: **1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **21,918,000**
- Tuberculosis case notification: *incidence rate: **90.35**/100,000
- Rate ratio people >55 / <15 years old: **11:1**
- Sputum smear positive cases: **8,591**
- Fraction of all pulmonary cases: **52**%
- Case detection rate: **52**%
- Treatment Success: **73**%
- Retreatment Cases: **8** % of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0.7**%
- WHO Control Category: **Countries implementing WHO TB control strategy in < 10 % of the population**
- Year N.T.P. was established: **1965**
- Year of Rifampicin Introduction: **1990**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **60**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **More than 15% of patients treate in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Sentinel sites**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **6** months

Culture Media: **Loewenstein-Jensen**

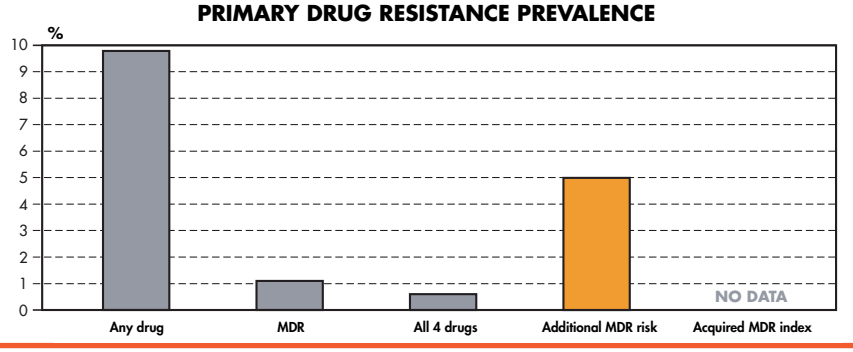
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **95.8**%

Specificity of RMP testing: **97.3**%

* Only primary drug resistance reported.

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	787	100				
SENSITIVE TO ALL 4 DRUGS	**710**	**90.2**				
ANY RESISTANCE	**77**	**9.8**				
Isoniazid (INH)	44	5.6				
Rifampicin (RMP)	13	1.7				
Ethambutol (EMB)	9	1.1				
Streptomycin (SM)	58	7.4				
MONORESISTANCE	**45**	**5.7**				
Isoniazid (INH)	13	1.7				
Rifampicin (RMP)	3	0.4				
Ethambutol (EMB)	0	0.0				
Streptomycin (SM)	29	3.7				
MULTIDRUG RESISTANCE	**9**	**1.1**				
INH + RMP	1	0.1				
INH + RMP + EMB	0	0.0				
INH + RMP + SM	3	0.4				
INH + RMP + EMB + SM	5	0.6				
OTHER PATTERNS	**23**	**2.9**				
INH + EMB	1	0.1				
INH + SM	19	2.4				
INH + EMB + SM	2	0.3				
RMP + EMB	1	0.1				
RMP + SM	0	0.0				
RMP + EMB + SM	0	0.0				
EMB + SM	0	0.0				
NUMBER OF DRUGS RESISTANT TO:						
0	710	90.2				
1	45	5.7				
2	22	2.8				
3	5	0.6				
4	**5**	**0.6**				

NETHERLANDS

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **15,503,000**
- Tuberculosis case notification: *incidence rate: **10.44**/100,000
- Rate ratio people >55 / <15 years old: **6:1**
- Sputum smear positive cases: **(not available)**
- Fraction of all pulmonary cases: **(not available)**
- Case detection rate: **(not available)**
- Treatment Success: **81**%
- Retreatment Cases: **7**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **10.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90 % of the population**
- Year N.T.P. was established: **1955**
- Year of Rifampicin Introduction: **1965**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

Culture Media: **Various**

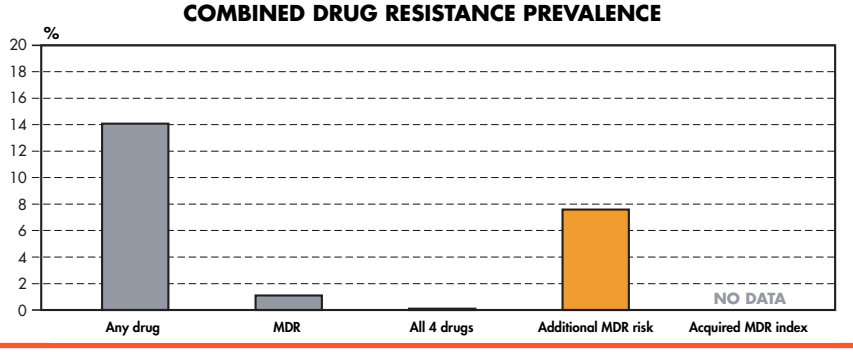
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **95.0**%

Specificity of RMP testing: **100.0**%

* Only combined data reported.

COMBINED DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested					1104	100
SENSITIVE TO ALL 4 DRUGS					**948**	**85.9**
ANY RESISTANCE					**156**	**14.1**
Isoniazid (INH)					95	8.6
Rifampicin (RMP)					13	1.2
Ethambutol (EMB)					4	0.4
Streptomycin (SM)					96	8.7
MONORESISTANCE					**110**	**10.0**
Isoniazid (INH)					49	4.4
Rifampicin (RMP)					1	0.1
Ethambutol (EMB)					0	0.0
Streptomycin (SM)					60	5.4
MULTIDRUG RESISTANCE					**12**	**1.1**
INH + RMP					10	0.9
INH + RMP + EMB					0	0.0
INH + RMP + SM					1	0.1
INH + RMP + EMB + SM					1	0.1
OTHER PATTERNS					**34**	**3.1**
INH + EMB					0	0.0
INH + SM					31	2.8
INH + EMB + SM					3	0.3
RMP + EMB					0	0.0
RMP + SM					0	0.0
RMP + EMB + SM					0	0.0
EMB + SM					0	0.0
NUMBER OF DRUGS RESISTANT TO:						
0					948	85.9
1					110	10.0
2					41	3.7
3					4	0.4
4					**1**	**0.1**

NEW ZEALAND

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **3,575,000**
- Tuberculosis case notification: *incidence rate: **8.59**/100,000
- Rate ratio people >55 / <15 years old: **24:1**
- Sputum smear positive cases: **47**
- Fraction of all pulmonary cases: **18**%
- Case detection rate: **29**%
- Treatment Success: **(not available)**
- Retreatment Cases: **3**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **6.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate <10/100,000**
- Year N.T.P. was established: **1950**
- Year of Rifampicin Introduction: **1969**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **96**%
- Use of Directly Observed Therapy: **Full treatment under DOT (<50% of patients)**
- Use of Fixed Dose Combination Tablets: **99**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

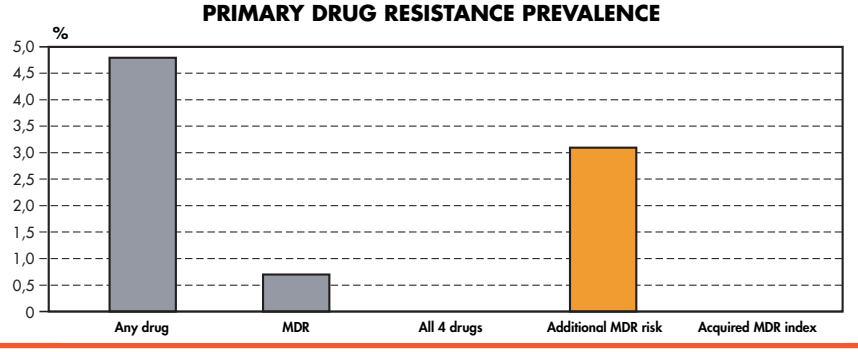
Culture Media: **BACTEC**

Drug Suceptibility Testing Method: **BACTEC**

Laboratory Accuracy: **97.5**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	418	100	19	100	437	100
SENSITIVE TO ALL 4 DRUGS	**398**	**95.2**	**18**	**94.7**	**416**	**95.2**
ANY RESISTANCE	**20**	**4.8**	**1**	**5.3**	**21**	**4.8**
Isoniazid (INH)	18	4.3	1	5.3	19	4.3
Rifampicin (RMP)	3	0.7	0	0.0	3	0.7
Ethambutol (EMB)	2	0.5	0	0.0	2	0.5
Streptomycin (SM)	4	1.0	0	0.0	4	0.9
MONORESISTANCE	**15**	**3.6**	**1**	**5.3**	**16**	**3.7**
Isoniazid (INH)	13	3.1	1	5.3	14	3.2
Rifampicin (RMP)	0	0.0	0	0.0	0	0.0
Ethambutol (EMB)	0	0.0	0	0.0	0	0.0
Streptomycin (SM)	2	0.5	0	0.0	2	0.5
MULTIDRUG RESISTANCE	**3**	**0.7**	**0**	**0.0**	**3**	**0.7**
INH + RMP	1	0.2	0	0.0	1	0.2
INH + RMP + EMB	1	0.2	0	0.0	1	0.2
INH + RMP + SM	1	0.2	0	0.0	1	0.2
INH + RMP + EMB + SM	0	0.0	0	0.0	0	0.0
OTHER PATTERNS	**2**	**0.5**	**0**	**0.0**	**2**	**0.5**
INH + EMB	1	0.2	0	0.0	1	0.2
INH + SM	1	0.2	0	0.0	1	0.2
INH + EMB + SM	0	0.0	0	0.0	0	0.0
RMP + EMB	0	0.0	0	0.0	0	0.0
RMP + SM	0	0.0	0	0.0	0	0.0
RMP + EMB + SM	0	0.0	0	0.0	0	0.0
EMB + SM	0	0.0	0	0.0	0	0.0
NUMBER OF DRUGS RESISTANT TO:						
0	398	95.2	18	94.7	416	95.2
1	15	3.6	1	5.3	16	3.7
2	3	0.7	0	0.0	3	0.7
3	2	0.5	0	0.0	2	0.5
4	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**

NORTHERN IRELAND

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **1,640,000**
- Tuberculosis case notification: *incidence rate: **4.60**/100,000
- Rate ratio people >55 / <15 years old: **7:1**
- Sputum smear positive cases: **32**
- Fraction of all pulmonary cases: **43**%
- Case detection rate: **(not available)**
- Treatment Success: **65**%
- Retreatment Cases: **9**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate <10/100,000**
- Year N.T.P. was established: **No NTP**
- Year of Rifampicin Introduction: **1969**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

Culture Media: **Loewenstein-Jensen and BACTEC**

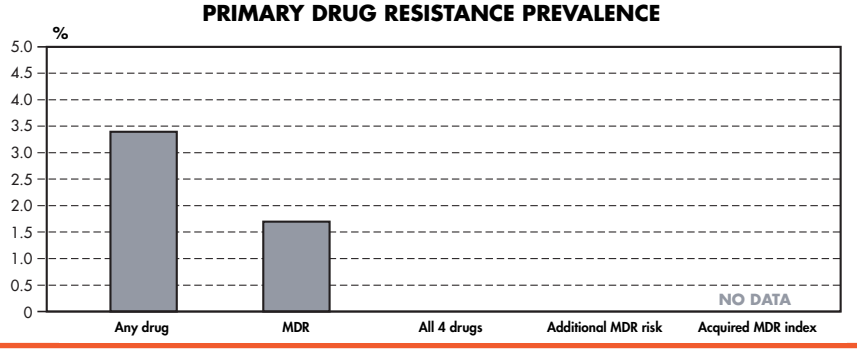
Drug Suceptibility Testing Method: **Resistance ratio method**

Laboratory Accuracy: **100.0**%

Specificity of RMP testing: **100.0**%

* Case notification and smear positive figures are those of the UK. Only new patients reported.

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	59	100				
SENSITIVE TO ALL 4 DRUGS	**57**	**96.6**				
ANY RESISTANCE	**2**	**3.4**				
Isoniazid (INH)	1	1.7				
Rifampicin (RMP)	1	1.7				
Ethambutol (EMB)	0	0.0				
Streptomycin (SM)	1	1.7				
MONORESISTANCE	**1**	**1.7**				
Isoniazid (INH)	0	0.0				
Rifampicin (RMP)	0	0.0				
Ethambutol (EMB)	0	0.0				
Streptomycin (SM)	1	1.7				
MULTIDRUG RESISTANCE	**1**	**1.7**				
INH + RMP	1	1.7				
INH + RMP + EMB	0	0.0				
INH + RMP + SM	0	0.0				
INH + RMP + EMB + SM	0	0.0				
OTHER PATTERNS	**0**	**0.0**				
INH + EMB	0	0.0				
INH + SM	0	0.0				
INH + EMB + SM	0	0.0				
RMP + EMB	0	0.0				
RMP + SM	0	0.0				
RMP + EMB + SM	0	0.0				
EMB + SM	0	0.0				
NUMBER OF DRUGS RESISTANT TO:						
0	57	96.6				
1	1	1.7				
2	1	1.7				
3	0	0.0				
4	**0**	**0.0**				

PERU

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **23,780,000**
- Tuberculosis case notification: *incidence rate: **197**/100,000
- Rate ratio people >55 / <15 years old: **9:1**
- Sputum smear positive cases: **32,096**
- Fraction of all pulmonary cases: **80**%
- Case detection rate: **78**%
- Treatment Success: **81**%
- Retreatment Cases: **15**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0.4**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90% of the population**
- Year N.T.P. was established: **1990**
- Year of Rifampicin Introduction: **1980**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Full treatment under DOT (>50% of patients)**
- Use of Fixed Dose Combination Tablets: **20**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **6**%

Study duration: **4** months

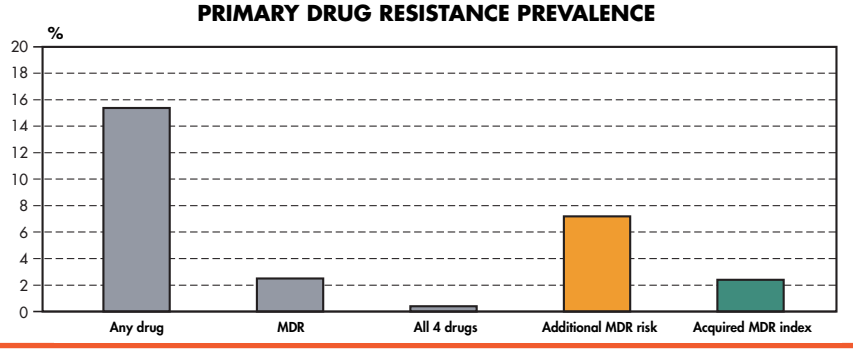
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **96.3**%

Specificity of RMP testing: **99.2**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	1500	100	458	100	*	100
SENSITIVE TO ALL 4 DRUGS	**1269**	**84.6**	**293**	**64.0**		**81.5**
ANY RESISTANCE	**231**	**15.4**	**165**	**36.0**		**18.5**
Isoniazid (INH)	113	7.5	109	23.8		10.0
Rifampicin (RMP)	69	4.6	93	20.3		7.0
Ethambutol (EMB)	24	1.6	28	6.1		2.3
Streptomycin (SM)	131	8.7	79	17.2		10.0
MONORESISTANCE	**152**	**10.1**	**74**	**16.2**		**11.0**
Isoniazid (INH)	47	3.1	23	5.0		3.4
Rifampicin (RMP)	23	1.5	16	3.5		1.8
Ethambutol (EMB)	6	0.4	3	0.7		0.4
Streptomycin (SM)	76	5.1	32	7.0		5.4
MULTIDRUG RESISTANCE	**37**	**2.5**	**72**	**15.7**		**4.5**
INH + RMP	17	1.1	32	7.0		2.0
INH + RMP + EMB	3	0.2	12	2.6		0.6
INH + RMP + SM	11	0.7	16	3.5		1.1
INH + RMP + EMB + SM	6	0.4	12	2.6		0.7
OTHER PATTERNS	**42**	**2.8**	**19**	**4.1**		**3.0**
INH + EMB	3	0.2	0	0.0		0.2
INH + SM	26	1.7	13	2.8		1.9
INH + EMB + SM	0	0.0	1	0.2		0.0
RMP + EMB	1	0.1	0	0.0		0.1
RMP + SM	7	0.5	5	1.1		0.6
RMP + EMB + SM	1	0.1	0	0.0		0.1
EMB + SM	4	0.3	0	0.0		0.2
NUMBER OF DRUGS RESISTANT TO:						
0	1269	84.6	293	64.0		81.5
1	152	10.1	74	16.2		11.0
2	58	3.9	50	10.9		4.9
3	15	1.0	29	6.3		1.8
4	**6**	**0.4**	**12**	**2.6**		**0.7**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

PORTUGAL

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **9,823,000**
- Tuberculosis case notification: *incidence rate: **56.77**/100,000
- Rate ratio people >55 / <15 years old: **15:1**
- Sputum smear positive cases: **2,287**
- Fraction of all pulmonary cases: **60**%
- Case detection rate: **76**%
- Treatment Success: **75**%
- Retreatment Cases: **12**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **6.7**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90 % of the population**
- Year N.T.P. was established: **1977**
- Year of Rifampicin Introduction: **1968**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **60**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **80**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **20**%

Study duration: **24** months

Culture Media: **Loewenstein-Jensen**

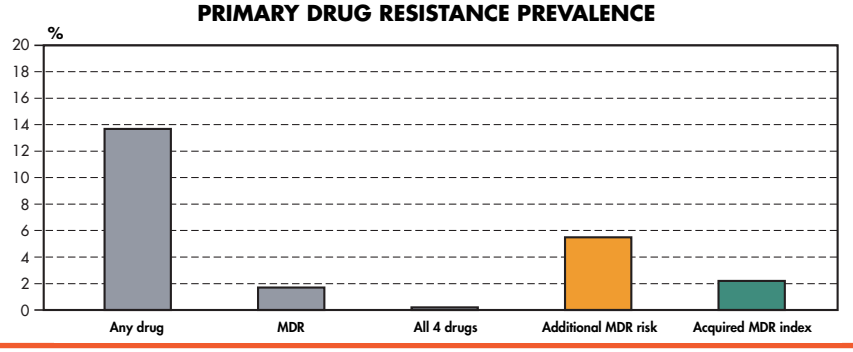
Drug Suceptibility Testing Method: **Modified Proportion Method**

Laboratory Accuracy: **98.0**%

Specificity of RMP testing: **100.0**%

* Ongoing survey

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	815	100	117	100	*	100
SENSITIVE TO ALL 4 DRUGS	**703**	**86.3**	**73**	**62.4**		**83.5**
ANY RESISTANCE	**112**	**13.7**	**44**	**37.6**		**16.5**
Isoniazid (INH)	58	7.1	35	29.9		9.8
Rifampicin (RMP)	15	1.8	22	18.8		3.8
Ethambutol (EMB)	2	0.2	8	6.8		1.0
Streptomycin (SM)	95	11.7	32	27.4		13.5
MONORESISTANCE	**68**	**8.3**	**14**	**12.0**		**8.8**
Isoniazid (INH)	15	1.8	5	4.3		2.1
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	53	6.5	9	7.7		6.6
MULTIDRUG RESISTANCE	**14**	**1.7**	**22**	**18.8**		**3.7**
INH + RMP	2	0.2	5	4.3		0.7
INH + RMP + EMB	0	0.0	2	1.7		0.2
INH + RMP + SM	10	1.2	9	7.7		2.0
INH + RMP + EMB + SM	2	0.2	6	5.1		0.8
OTHER PATTERNS	**30**	**3.7**	**8**	**6.8**		**4.1**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	29	3.6	8	6.8		3.9
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	1	0.1	0	0.0		0.1
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	703	86.3	73	62.4		83.5
1	68	8.3	14	12.0		8.8
2	32	3.9	13	11.1		4.8
3	10	1.2	11	9.4		2.2
4	**2**	**0.2**	**6**	**5.1**		**0.8**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

PUERTO RICO

YEAR OF SURVEY: **1994-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **3,674,000**
- Tuberculosis case notification: *incidence rate: **7.16**/100,000
- Rate ratio people >55 / <15 years old: **13:1**
- Sputum smear positive cases: **126**
- Fraction of all pulmonary cases: **54**%
- Case detection rate: **95**%
- Treatment Success: **51**%
- Retreatment Cases: **6**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **18.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate <10/100,000**
- Year N.T.P. was established: **1953**
- Year of Rifampicin Introduction: **1981**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **90**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **36** months

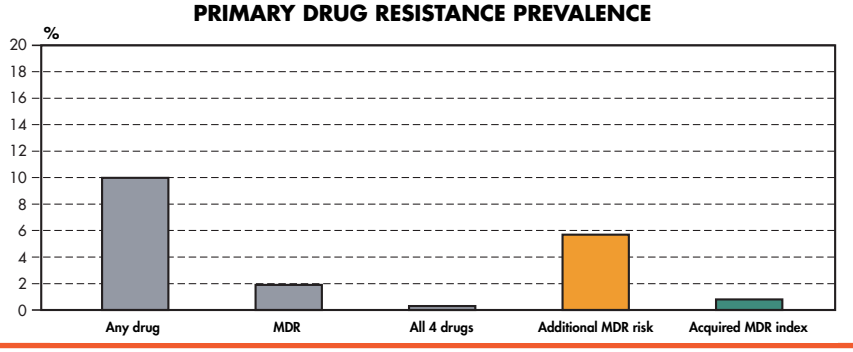
Culture Media: **BACTEC**

Drug Suceptibility Testing Method: **Proportion method and BACTEC**

Laboratory Accuracy: **100.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	369	100	22	100	391	100
SENSITIVE TO ALL 4 DRUGS	**332**	**90.0**	**16**	**72.7**	**348**	**89.0**
ANY RESISTANCE	**37**	**10.0**	**6**	**27.3**	**43**	**11.0**
Isoniazid (INH)	25	6.8	5	22.7	30	7.7
Rifampicin (RMP)	10	2.7	4	18.2	14	3.6
Ethambutol (EMB)	11	3.0	3	13.6	14	3.6
Streptomycin (SM)	9	2.4	2	9.1	11	2.8
MONORESISTANCE	**26**	**7.0**	**1**	**4.5**	**27**	**6.9**
Isoniazid (INH)	15	4.1	1	4.5	16	4.1
Rifampicin (RMP)	2	0.5	0	0.0	2	0.5
Ethambutol (EMB)	5	1.4	0	0.0	5	1.3
Streptomycin (SM)	4	1.1	0	0.0	4	1.0
MULTIDRUG RESISTANCE	**7**	**1.9**	**3**	**13.6**	**10**	**2.6**
INH + RMP	1	0.3	2	9.1	3	0.8
INH + RMP + EMB	2	0.5	0	0.0	2	0.5
INH + RMP + SM	3	0.8	0	0.0	3	0.8
INH + RMP + EMB + SM	1	0.3	1	4.5	2	0.5
OTHER PATTERNS	**4**	**1.1**	**2**	**9.1**	**6**	**1.5**
INH + EMB	3	0.8	0	0.0	3	0.8
INH + SM	0	0.0	0	0.0	0	0.0
INH + EMB + SM	0	0.0	1	4.5	1	0.3
RMP + EMB	0	0.0	1	4.5	1	0.3
RMP + SM	1	0.3	0	0.0	1	0.3
RMP + EMB + SM	0	0.0	0	0.0	0	0.0
EMB + SM	0	0.0	0	0.0	0	0.0
NUMBER OF DRUGS RESISTANT TO:						
0	332	90.0	16	72.7	348	89.0
1	26	7.0	1	4.5	27	6.9
2	5	1.4	3	13.6	8	2.0
3	5	1.4	1	4.5	6	1.5
4	**1**	**0.3**	**1**	**4.5**	**2**	**0.5**

REPUBLIC OF KOREA

YEAR OF SURVEY: **1994**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **44,453,000**
- Tuberculosis case notification: *incidence rate: **80.50**/100,000
- Rate ratio people >55 / <15 years old: **93:1**
- Sputum smear positive cases: **13,266**
- Fraction of all pulmonary cases: **37**%
- Case detection rate: **68**%
- Treatment Success: **81**%
- Retreatment Cases: **6**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in 10-90% of the population**
- Year N.T.P. was established: **1962**
- Year of Rifampicin Introduction: **1984**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **96**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **3** months

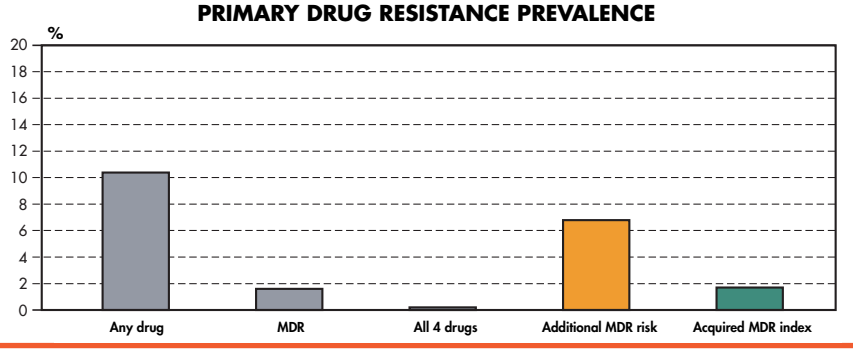
Culture Media: **Ogawa**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **95.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	2486	100	189	100	*	100
SENSITIVE TO ALL 4 DRUGS	**2228**	**89.6**	**89**	**47.1**		**87.1**
ANY RESISTANCE	**258**	**10.4**	**100**	**52.9**		**12.9**
Isoniazid (INH)	192	7.7	86	45.5		10.0
Rifampicin (RMP)	55	2.2	61	32.3		4.0
Ethambutol (EMB)	64	2.6	56	29.6		4.2
Streptomycin (SM)	68	2.7	28	14.8		3.5
MONORESISTANCE	**171**	**6.9**	**27**	**14.3**		**7.3**
Isoniazid (INH)	113	4.5	19	10.1		4.9
Rifampicin (RMP)	8	0.3	3	1.6		0.4
Ethambutol (EMB)	12	0.5	2	1.1		0.5
Streptomycin (SM)	38	1.5	3	1.6		1.5
MULTIDRUG RESISTANCE	**39**	**1.6**	**52**	**27.5**		**3.1**
INH + RMP	13	0.5	8	4.2		0.7
INH + RMP + EMB	18	0.7	27	14.3		1.5
INH + RMP + SM	4	0.2	4	2.1		0.3
INH + RMP + EMB + SM	4	0.2	13	6.9		0.6
OTHER PATTERNS	**48**	**1.9**	**21**	**11.1**		**2.5**
INH + EMB	19	0.8	9	4.8		1.0
INH + SM	17	0.7	6	3.2		0.8
INH + EMB + SM	4	0.2	0	0.0		0.2
RMP + EMB	7	0.3	4	2.1		0.4
RMP + SM	1	0.0	1	0.5		0.1
RMP + EMB + SM	0	0.0	1	0.5		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	2228	89.6	89	47.1		87.1
1	171	6.9	27	14.3		7.3
2	57	2.3	28	14.8		3.0
3	26	1.0	32	16.9		2.0
4	**4**	**0.2**	**13**	**6.9**		**0.6**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

ROMANIA

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **22,835,000**
- Tuberculosis case notification: *incidence rate: **101.91**/100,000
- Rate ratio people >55 / <15 years old: **4:1**
- Sputum smear positive cases: **10,469**
- Fraction of all pulmonary cases: **56**%
- Case detection rate: **85**%
- Treatment Success: **38**%
- Retreatment Cases: **7**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **1.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1995**
- Year of Rifampicin Introduction: **1975**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **80**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

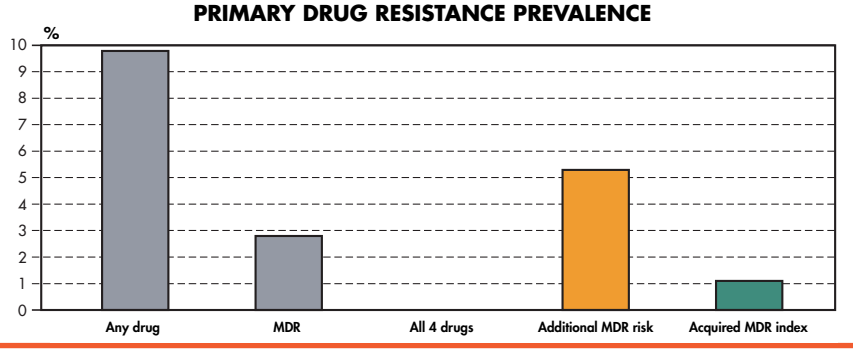
Culture Media: **TB-glut and Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Absolute concentration method**

Laboratory Accuracy: **90.1**%

Specificity of RMP testing: **96.8**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	1636	100	1521	100	*	0100
SENSITIVE TO ALL 4 DRUGS	**1476**	**90.2**	**969**	**63.7**		**88.2**
ANY RESISTANCE	**160**	**9.8**	**552**	**36.3**		**11.8**
Isoniazid (INH)	121	7.4	481	31.6		9.2
Rifampicin (RMP)	55	3.4	249	16.4		4.3
Ethambutol (EMB)	27	1.7	41	2.7		1.7
Streptomycin (SM)	54	3.3	218	14.3		4.1
MONORESISTANCE	**87**	**5.3**	**254**	**16.7**		**6.2**
Isoniazid (INH)	52	3.2	188	12.4		3.9
Rifampicin (RMP)	8	0.5	25	1.6		0.6
Ethambutol (EMB)	27	1.7	41	2.7		1.7
Streptomycin (SM)	0	0.0	0	0.0		0.0
MULTIDRUG RESISTANCE	**45**	**2.8**	**219**	**14.4**		**3.6**
INH + RMP	17	1.0	80	5.3		1.4
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	28	1.7	139	9.1		2.3
INH + RMP + EMB + SM	0	0.0	0	0.0		0.0
OTHER PATTERNS	**26**	**1.6**	**79**	**5.2**		**1.9**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	24	1.5	74	4.9		1.7
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	2	0.1	5	0.3		0.1
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	1476	90.2	969	63.7		88.2
1	87	5.3	254	16.7		6.2
2	43	2.6	159	10.5		3.2
3	28	1.7	139	9.1		2.3
4	**0**	**0.0**	**0**	**0.0**		**0.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

RUSSIA (Ivanovo Oblast)

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **1,271,100**
- Tuberculosis case notification: *incidence rate: **52.10**/100,000
- Rate ratio people >55 / <15 years old: **33:1**
- Sputum smear positive cases: **344**
- Fraction of all pulmonary cases: **47**%
- Case detection rate: **57**%
- Treatment Success: **70**%
- Retreatment Cases: **14**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1995**
- Year of Rifampicin Introduction: **1987**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Full treatment under DOT (>50% of patients)**
- Use of Fixed Dose Combination Tablets: **100**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Province**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

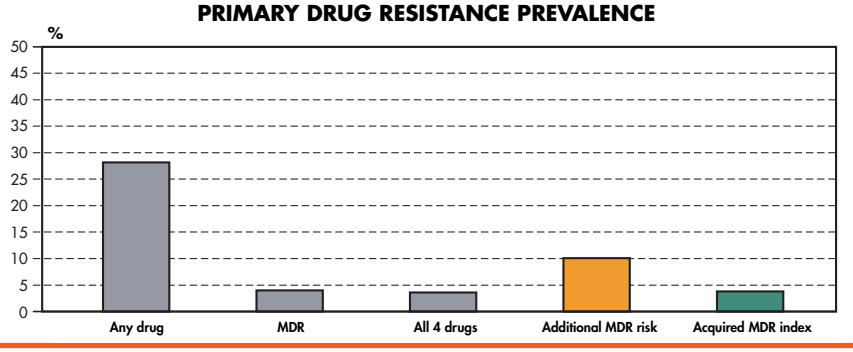
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **95.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	248	100	33	100	*	100
SENSITIVE TO ALL 4 DRUGS	**178**	**71.8**	**0**	**.0**		**61.7**
ANY RESISTANCE	**70**	**28.2**	**33**	**100.0**		**38.3**
Isoniazid (INH)	32	12.9	18	54.5		18.7
Rifampicin (RMP)	13	5.2	18	54.5		12.1
Ethambutol (EMB)	16	6.5	9	27.3		9.4
Streptomycin (SM)	66	26.6	16	48.5		29.7
MONORESISTANCE	**38**	**15.3**	**15**	**45.5**		**19.5**
Isoniazid (INH)	3	1.2	5	15.2		3.2
Rifampicin (RMP)	1	0.4	5	15.2		2.5
Ethambutol (EMB)	0	0.0	2	6.1		0.8
Streptomycin (SM)	34	13.7	3	9.1		13.1
MULTIDRUG RESISTANCE	**10**	**4.0**	**9**	**27.3**		**7.3**
INH + RMP	0	0.0	2	6.1		0.8
INH + RMP + EMB	0	0.0	1	3.0		0.4
INH + RMP + SM	1	0.4	4	12.1		2.0
INH + RMP + EMB + SM	9	3.6	2	6.1		4.0
OTHER PATTERNS	**22**	**8.9**	**9**	**27.3**		**11.4**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	14	5.6	3	9.1		6.1
INH + EMB + SM	5	2.0	1	3.0		2.2
RMP + EMB	0	0.0	2	6.1		0.8
RMP + SM	1	0.4	2	6.1		1.2
RMP + EMB + SM	1	0.4	0	0.0		0.3
EMB + SM	1	0.4	1	3.0		0.8
NUMBER OF DRUGS RESISTANT TO:						
0	178	71.8	0	0.0		61.7
1	38	15.3	15	45.5		19.5
2	16	6.5	10	30.3		9.8
3	7	2.8	6	18.2		5.0
4	**9**	**3.6**	**2**	**6.1**		**4.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

SCOTLAND

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **5,210,000**
- Tuberculosis case notification: *incidence rate: **10.60**/100,000
- Rate ratio people >55 / <15 years old: **33:1**
- Sputum smear positive cases: **(not available)**
- Fraction of all pulmonary cases: **(not available)**
- Case detection rate: **(not available)**
- Treatment Success: **65**%
- Retreatment Cases: **4**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **2.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **No NTP**
- Year of Rifampicin Introduction: **1975**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **100**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

Culture Media: **BACTEC**

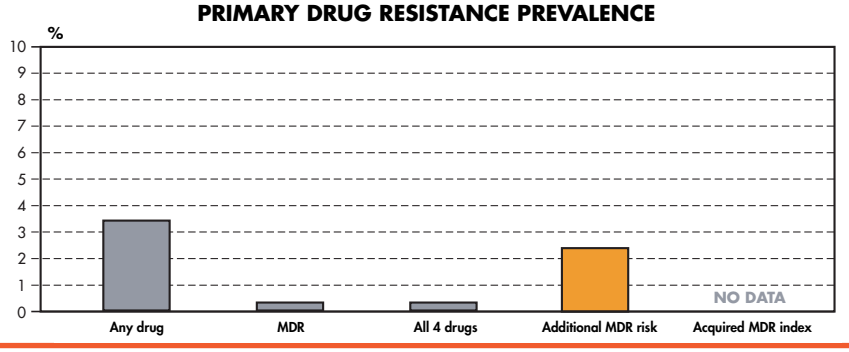
Drug Suceptibility Testing Method: **BACTEC**

Laboratory Accuracy: **(not available)**

Specificity of RMP testing: **(not available)**

*** Case notification rates are those of the UK. Only new patients reported.**

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	290	100				
SENSITIVE TO ALL 4 DRUGS	**280**	**96.6**				
ANY RESISTANCE	**10**	**3.4**				
Isoniazid (INH)	8	2.8				
Rifampicin (RMP)	1	0.3				
Ethambutol (EMB)	1	0.3				
Streptomycin (SM)	1	0.3				
MONORESISTANCE	**7**	**2.4**				
Isoniazid (INH)	7	2.4				
Rifampicin (RMP)	0	0.0				
Ethambutol (EMB)	0	0.0				
Streptomycin (SM)	0	0.0				
MULTIDRUG RESISTANCE	**1**	**0.3**				
INH + RMP	0	0.0				
INH + RMP + EMB	0	0.0				
INH + RMP + SM	0	0.0				
INH + RMP + EMB + SM	1	0.3				
OTHER PATTERNS	**0**	**0.0**				
INH + EMB	0	0.0				
INH + SM	0	0.0				
INH + EMB + SM	0	0.0				
RMP + EMB	0	0.0				
RMP + SM	0	0.0				
RMP + EMB + SM	0	0.0				
EMB + SM	0	0.0				
NUMBER OF DRUGS RESISTANT TO:						
0	280	96.6				
1	7	2.4				
2	0	0.0				
3	0	0.0				
4	**1**	**0.3**				

SIERRA LEONE

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **4,509,000**
- Tuberculosis case notification: *incidence rate: **42.44**/100,000
- Rate ratio people >55 / <15 years old: **1:1**
- Sputum smear positive cases: **1,454**
- Fraction of all pulmonary cases: **81**%
- Case detection rate: **43**%
- Treatment Success: **76**%
- Retreatment Cases: **27**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **4.5**%
- WHO Control Category: **Countries implementing WHO TB control strategy in 10-90% of the population**
- Year N.T.P. was established: **1990**
- Year of Rifampicin Introduction: **1985**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **70**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **95**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Nearly countrywide**

Sampling Method: **All cases**

Sampling Fraction: **15**%

Study duration: **24** months

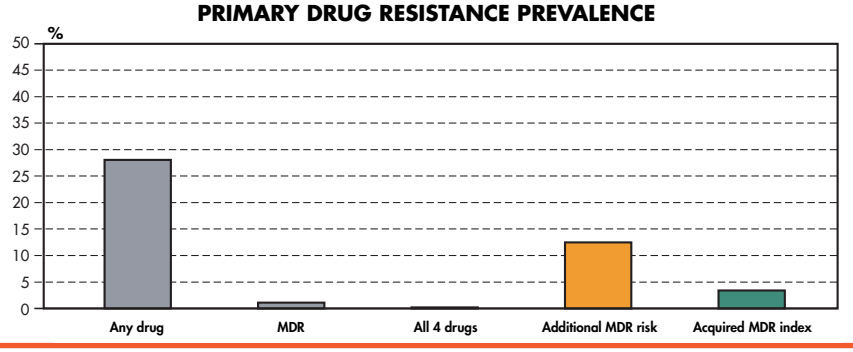
Culture Media: **Loewenstein-Jensen and others**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **95.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	463	100	172	100	*	100
SENSITIVE TO ALL 4 DRUGS	**333**	**71.9**	**81**	**47.1**		**65.2**
ANY RESISTANCE	**130**	**28.1**	**91**	**52.9**		**34.8**
Isoniazid (INH)	62	13.4	74	43.0		21.4
Rifampicin (RMP)	6	1.3	25	14.5		4.9
Ethambutol (EMB)	11	2.4	15	8.7		4.1
Streptomycin (SM)	111	24.0	73	42.4		28.9
MONORESISTANCE	**77**	**16.6**	**28**	**16.3**		**16.5**
Isoniazid (INH)	12	2.6	13	7.6		3.9
Rifampicin (RMP)	1	0.2	1	0.6		0.3
Ethambutol (EMB)	3	0.6	0	0.0		0.5
Streptomycin (SM)	61	13.2	14	8.1		11.8
MULTIDRUG RESISTANCE	**5**	**1.1**	**22**	**12.8**		**4.2**
INH + RMP	2	0.4	2	1.2		0.6
INH + RMP + EMB	1	0.2	2	1.2		0.5
INH + RMP + SM	1	0.2	6	3.5		1.1
INH + RMP + EMB + SM	1	0.2	12	7.0		2.0
OTHER PATTERNS	**48**	**10.4**	**41**	**23.8**		**14.0**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	42	9.1	38	22.1		12.6
INH + EMB + SM	3	0.6	1	0.6		0.6
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	2	1.2		0.3
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	3	0.6	0	0.0		0.5
NUMBER OF DRUGS RESISTANT TO:						
0	333	71.9	81	47.1		65.2
1	77	16.6	28	16.3		16.5
2	47	10.2	42	24.4		14.0
3	5	1.1	9	5.2		2.2
4	**1**	**0.2**	**12**	**7.0**		**2.0**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

SPAIN (Barcelona)

YEAR OF SURVEY: **1995-1996**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **1,650,000**
- Tuberculosis case notification: *incidence rate: **58.20**/100,000
- Rate ratio people >55 / <15 years old: **23:1**
- Sputum smear positive cases: **363**
- Fraction of all pulmonary cases: **30**%
- Case detection rate: **60**%
- Treatment Success: **65**%
- Retreatment Cases: **20**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **28.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1982**
- Year of Rifampicin Introduction: **1968**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **70**%
- Use of Directly Observed Therapy: **Full treatment under DOT (<50% of patients)**
- Use of Fixed Dose Combination Tablets: **50**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Citywide**

Sampling Method: **Cluster**

Sampling Fraction: **65**%

Study duration: **20** months

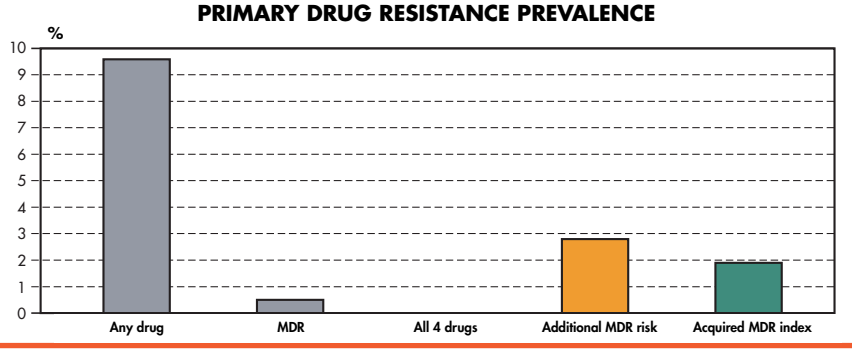
Culture Media: **Loewenstein-Jensen and BACTEC**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **96.0**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	218	100	44	100	*	100
SENSITIVE TO ALL 4 DRUGS	**197**	**90.4**	**31**	**70.5**		**87.1**
ANY RESISTANCE	**21**	**9.6**	**13**	**29.5**		**12.9**
Isoniazid (INH)	7	3.2	12	27.3		8.4
Rifampicin (RMP)	2	0.9	9	20.5		2.7
Ethambutol (EMB)	4	1.8	3	6.8		2.1
Streptomycin (SM)	10	4.6	8	18.2		3.1
MONORESISTANCE	**19**	**8.7**	**4**	**9.1**		**8.5**
Isoniazid (INH)	5	2.3	3	6.8		4.2
Rifampicin (RMP)	1	0.5	0	0.0		0.6
Ethambutol (EMB)	4	1.8	0	0.0		0.6
Streptomycin (SM)	9	4.1	1	2.3		3.1
MULTIDRUG RESISTANCE	**1**	**0.5**	**9**	**20.5**		**2.0**
INH + RMP	1	0.5	2	4.5		0.8
INH + RMP + EMB	0	0.0	0	0.0		0.2
INH + RMP + SM	0	0.0	4	9.1		0.3
INH + RMP + EMB + SM	0	0.0	3	6.8		0.7
OTHER PATTERNS	**1**	**0.5**	**0**	**0.0**		**2.6**
INH + EMB	0	0.0	0	0.0		0.2
INH + SM	1	0.5	0	0.0		1.8
INH + EMB + SM	0	0.0	0	0.0		0.3
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.1
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.2
NUMBER OF DRUGS RESISTANT TO:						
0	197	90.4	31	70.5		87.1
1	19	8.7	4	9.1		8.4
2	2	0.9	2	4.5		3.0
3	0	0.0	4	9.1		0.8
4	**0**	**0.0**	**3**	**6.8**		**0.7**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

SWAZILAND

YEAR OF SURVEY: **1994-1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **855,000**
- Tuberculosis case notification: *incidence rate: **240.35**/100,000
- Rate ratio people >55 / <15 years old: **51:1**
- Sputum smear positive cases: **660**
- Fraction of all pulmonary cases: **49**%
- Case detection rate: **86**%
- Treatment Success: **(not available)**
- Retreatment Cases: **13**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **35.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1990**
- Year of Rifampicin Introduction: **1980**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Full treatment under DOT (<50% of patients)**
- Use of Fixed Dose Combination Tablets: **100**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **20**%

Study duration: **18** months

Culture Media: **Loewenstein-Jensen**

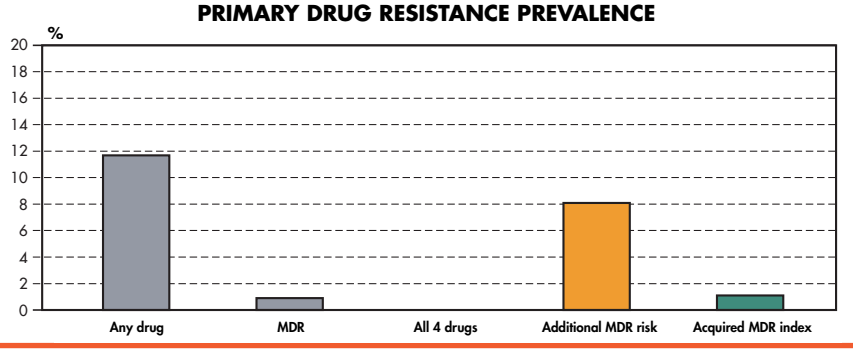
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **94.0**%

Specificity of RMP testing: **100.0**%

* Children under 15 years of age not reported.

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	334	100	44	100	*	100
SENSITIVE TO ALL 4 DRUGS	**295**	**88.3**	**35**	**79.5**		**87.2**
ANY RESISTANCE	**39**	**11.7**	**9**	**20.5**		**12.8**
Isoniazid (INH)	30	9.0	6	13.6		9.6
Rifampicin (RMP)	3	0.9	4	9.1		1.9
Ethambutol (EMB)	3	0.9	2	4.5		1.4
Streptomycin (SM)	24	7.2	7	15.9		8.3
MONORESISTANCE	**22**	**6.6**	**4**	**9.1**		**6.9**
Isoniazid (INH)	13	3.9	1	2.3		3.7
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	1	0.3	0	0.0		0.3
Streptomycin (SM)	8	2.4	3	6.8		2.9
MULTIDRUG RESISTANCE	**3**	**0.9**	**4**	**9.1**		**1.9**
INH + RMP	0	0.0	1	2.3		0.3
INH + RMP + EMB	1	0.3	0	0.0		0.3
INH + RMP + SM	2	0.6	1	2.3		0.8
INH + RMP + EMB + SM	0	0.0	2	4.5		0.6
OTHER PATTERN	**14**	**4.2**	**1**	**2.3**		**4.0**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	13	3.9	1	2.3		3.7
INH + EMB + SM	1	0.3	0	0.0		0.3
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	295	88.3	35	79.5		87.2
1	22	6.6	4	9.1		6.9
2	13	3.9	2	4.5		4.0
3	4	1.2	1	2.3		1.3
4	**0**	**0.0**	**2**	**4.5**		**0.6**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

THAILAND

YEAR OF SURVEY: **1996-1997**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **58,791,000**
- Tuberculosis case notification: *incidence rate: **77.27**/100,000
- Rate ratio people >55 / <15 years old: **(not available)**
- Sputum smear positive cases: **20,273**
- Fraction of all pulmonary cases: **47**%
- Case detection rate: **44**%
- Treatment Success: **58**%
- Retreatment Cases: **3**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **20.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate >10/100,000**
- Year N.T.P. was established: **1966**
- Year of Rifampicin Introduction: **1985**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **Virtually no DOT**
- Use of Fixed Dose Combination Tablets: **20**%
- Treatment In Private Sector: **(non available)**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Proportionate clusters**

Sampling Fraction: **13**%

Study duration: **6** months

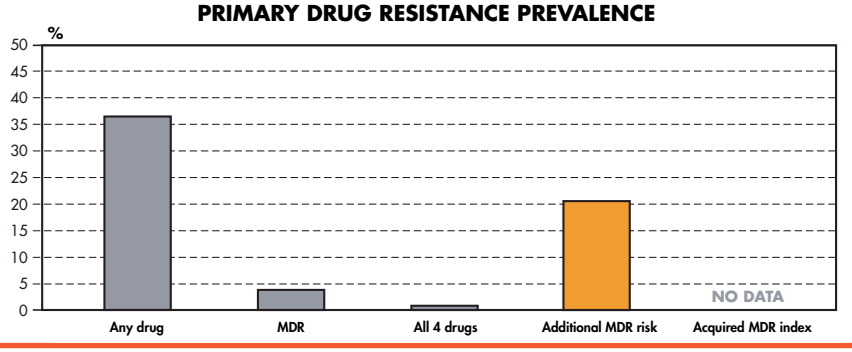
Culture Media: **Loewenstein-Jensen**

Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **89.2**%

Specificity of RMP testing: **pending**

PRIMARY DRUG RESISTANCE PREVALENCE



These results are preliminary and should not be formally cited without special permission by WHO and the authors of the survey.

PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	131	100	0	100		100
SENSITIVE TO ALL 4 DRUGS	**83**	**63.4**				
ANY RESISTANCE	**48**	**36.6**				
Isoniazid (INH)	15	11.5				
Rifampicin (RMP)	22	16.8				
Ethambutol (EMB)	13	9.9				
Streptomycin (SM)	24	18.3				
MONORESISTANCE	**28**	**21.4**				
Isoniazid (INH)	6	4.6				
Rifampicin (RMP)	9	6.9				
Ethambutol (EMB)	3	2.3				
Streptomycin (SM)	10	7.6				
MULTIDRUG RESISTANCE	**5**	**3.8**				
INH + RMP	1	0.8				
INH + RMP + EMB	1	0.8				
INH + RMP + SM	2	1.5				
INH + RMP + EMB + SM	1	0.8				
OTHER PATTERNS	**15**	**11.5**				
INH + EMB	2	1.5				
INH + SM	2	1.5				
INH + EMB + SM	0	0.0				
RMP + EMB	2	1.5				
RMP + SM	5	3.8				
RMP + EMB + SM	1	0.8				
EMB + SM	3	2.3				
NUMBER OF DRUGS RESISTANT TO:						
0	83	63.4				
1	28	21.4				
2	15	11.5				
3	4	3.1				
4	**1**	**0.8**				

UNITED STATES OF AMERICA

YEAR OF SURVEY: **1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **262,755,000**
- Tuberculosis case notification: *incidence rate: **8.68**/100,000
- Rate ratio people >55 / <15 years old: **8:1**
- Sputum smear positive cases: **8,012**
- Fraction of all pulmonary cases: **43**%
- Case detection rate: **68**%
- Treatment Success: **75**%
- Retreatment Cases: **7**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **9.0**%
- WHO Control Category: **Countries not accepting WHO TB control estrategy and TB notification rate <10/100,000**
- Year N.T.P. was established: **1953**
- Year of Rifampicin Introduction: **1971**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **95**%
- Use of Directly Observed Therapy: **Full treatment under DOT (<50% of patients)**
- Use of Fixed Dose Combination Tablets: **3**%
- Treatment In Private Sector: **More than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **12** months

Culture Media: **Various**

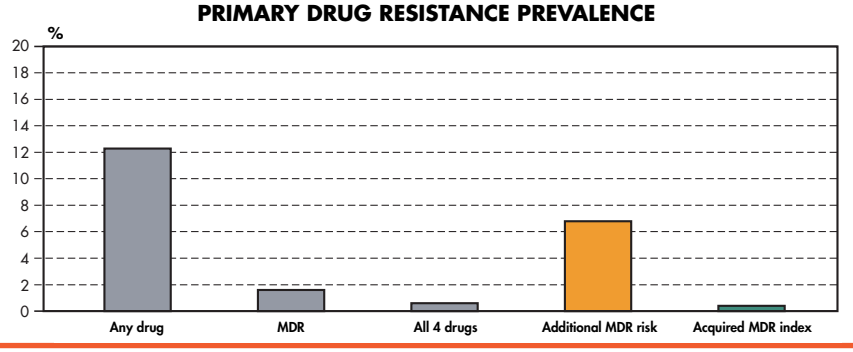
Drug Suceptibility Testing Method: **Various**

Laboratory Accuracy: **99.8**%

Specificity of RMP testing: **99.6**%

*** 18,292 cases reported, but only the 14,344 with DST results for the 4 drugs were analysed.**

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	13511	100	833	100	14,344	100
SENSITIVE TO ALL 4 DRUGS	**11854**	**87.7**	**636**	**76.4**	**12,490**	**87.1**
ANY RESISTANCE	**1657**	**12.3**	**197**	**23.6**	**1,854**	**12.9**
Isoniazid (INH)	1050	7.8	150	18.0	1,200	8.4
Rifampicin (RMP)	318	2.4	70	8.4	388	2.7
Ethambutol (EMB)	269	2.0	39	4.7	308	2.1
Streptomycin (SM)	833	6.2	92	11.0	925	6.4
MONORESISTANCE	**1102**	**8.2**	**104**	**12.5**	**1,206**	**8.4**
Isoniazid (INH)	536	4.0	60	7.2	596	4.2
Rifampicin (RMP)	80	0.6	8	1.0	88	0.6
Ethambutol (EMB)	74	0.5	6	0.7	80	0.6
Streptomycin (SM)	412	3.0	30	3.6	442	3.1
MULTIDRUG RESISTANCE	**222**	**1.6**	**59**	**7.1**	**281**	**2.0**
INH + RMP	85	0.6	22	2.6	107	0.7
INH + RMP + EMB	21	0.2	8	1.0	29	0.2
INH + RMP + SM	31	0.2	12	1.4	33	0.3
INH + RMP + EMB + SM	85	0.6	17	2.0	102	0.7
OTHER PATTERNS	**333**	**2.5**	**34**	**4.1**	**367**	**2.6**
INH + EMB	24	0.2	1	0.1	25	0.2
INH + SM	236	1.7	25	3.0	261	1.8
INH + EMB + SM	32	0.2	5	0.6	37	0.3
RMP + EMB	4	0.0	0	0.0	4	0.0
RMP + SM	8	0.1	1	0.1	9	0.1
RMP + EMB + SM	4	0.0	2	0.2	6	0.0
EMB + SM	25	0.2	0	0.0	25	0.2
NUMBER OF DRUGS RESISTANT TO:						
0	11854	87.7	636	76.4	12,490	87.1
1	1102	8.2	104	12.5	1,206	8.4
2	382	2.8	49	5.9	431	3.0
3	88	0.7	27	3.2	115	0.8
4	**85**	**0.6**	**17**	**2.0**	**102**	**0.7**

VIET NAM

YEAR OF SURVEY: **1996-1997**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **74,545,000**
- Tuberculosis case notification: *incidence rate: **74.77**/100,000
- Rate ratio people >55 / <15 years old: **1:1**
- Sputum smear positive cases: **37,550**
- Fraction of all pulmonary cases: **82**%
- Case detection rate: **67**%
- Treatment Success: **88**%
- Retreatment Cases: **11**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **1.2**%
- WHO Control Category: **Countries implementing WHO TB control strategy in 10-90% of the population**
- Year N.T.P. was established: **1957**
- Year of Rifampicin Introduction: **1976**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **49**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **49**%
- Treatment In Private Sector: **Less than 15% of patients treated in private sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Countrywide**

Sampling Method: **Random clusters**

Sampling Fraction: **100**%

Study duration: **10** months

Culture Media: **Loewenstein-Jensen**

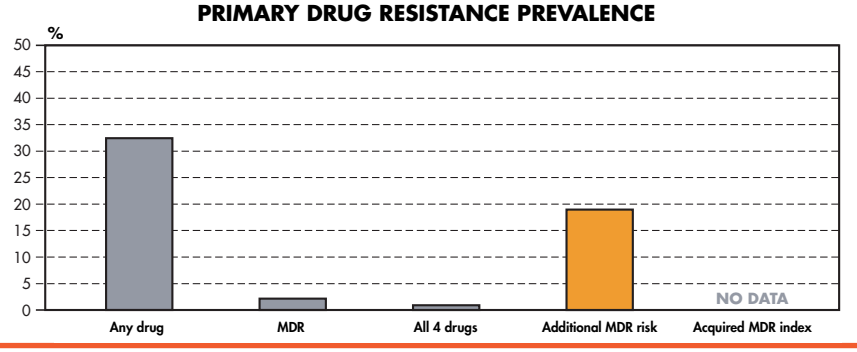
Drug Suceptibility Testing Method: **Proportion method**

Laboratory Accuracy: **92.7**%

Specificity of RMP testing: **96.9**%

* These results are preliminary and should not be formally cited.

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	640	100				
SENSITIVE TO ALL 4 DRUGS	**432**	**67.5**				
ANY RESISTANCE	**208**	**32.5**				
Isoniazid (INH)	128	20.0				
Rifampicin (RMP)	23	3.6				
Ethambutol (EMB)	7	1.1				
Streptomycin (SM)	154	24.1				
MONORESISTANCE	**122**	**19.1**				
Isoniazid (INH)	43	6.7				
Rifampicin (RMP)	7	1.1				
Ethambutol (EMB)	1	0.2				
Streptomycin (SM)	71	11.1				
MULTIDRUG RESISTANCE	**15**	**2.3**				
INH + RMP	3	0.5				
INH + RMP + EMB	0	0.0				
INH + RMP + SM	6	0.9				
INH + RMP + EMB + SM	6	0.9				
OTHER PATTERNS	**71**	**11.1**				
INH + EMB	0	0.0				
INH + SM	70	10.9				
INH + EMB + SM	0	0.0				
RMP + EMB	0	0.0				
RMP + SM	1	0.2				
RMP + EMB + SM	0	0.0				
EMB + SM	0	0.0				
NUMBER OF DRUGS RESISTANT TO:						
0	432	67.5				
1	122	19.1				
2	74	11.6				
3	6	0.9				
4	**6**	**0.9**				

ZIMBABWE

YEAR OF SURVEY: **1994-1995**

PROFILE OF THE COUNTRY OR REGION AND ITS CONTROL PROGRAM, 1995

- Population: **11,261,000**
- Tuberculosis case notification: *incidence rate: **273.79**/100,000
- Rate ratio people >55 / <15 years old: **15:1**
- Sputum smear positive cases: **8,965**
- Fraction of all pulmonary cases: **36**%
- Case detection rate: **85**%
- Treatment Success: **52**%
- Retreatment Cases: **7**% of total smear positive patients registering for treatment
- HIV Co-Infection Rate: **60.0**%
- WHO Control Category: **Countries implementing WHO TB control strategy in > 90% of the population**
- Year N.T.P. was established: **1959**
- Year of Rifampicin Introduction: **1990**
- Standardized Regimens: **Yes**
- Use of Short Course Chemotherapy: **100**%
- Use of Directly Observed Therapy: **DOT during the initial phase only**
- Use of Fixed Dose Combination Tablets: **0**%
- Treatment In Private Sector: **Virtually all patients treated in the public sector**

CHARACTERISTICS OF THE SURVEY/SURVEILLANCE PROGRAM

Target Area: **Nearly countrywide**

Sampling Method: **All cases**

Sampling Fraction: **100**%

Study duration: **30** months

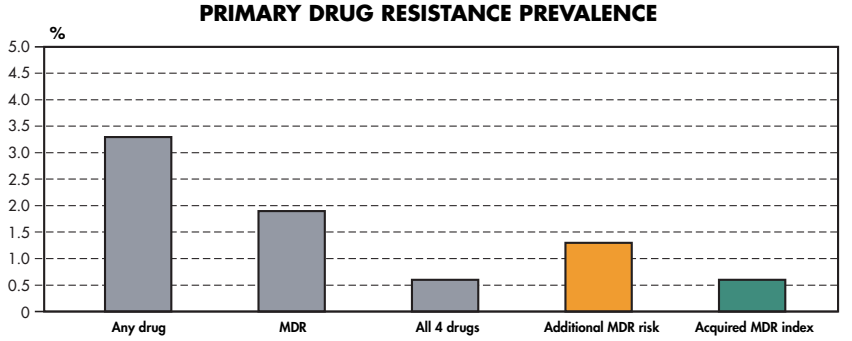
Culture Media: **Ogawa**

Drug Suceptibility Testing Method: **Various**

Laboratory Accuracy: **96.7**%

Specificity of RMP testing: **100.0**%

PRIMARY DRUG RESISTANCE PREVALENCE



PREVALENCE OF DRUG RESISTANCE

	Primary		Acquired		Combined	
	N	%	N	%	N	%
Total number of strains tested	676	100	36	100	*	100
SENSITIVE TO ALL 4 DRUGS	**654**	**96.7**	**31**	**86.1**		**96.0**
ANY RESISTANCE	**22**	**3.3**	**5**	**13.9**		**4.0**
Isoniazid (INH)	22	3.3	5	13.9		4.0
Rifampicin (RMP)	13	1.9	3	8.3		2.4
Ethambutol (EMB)	4	0.6	0	0.0		0.5
Streptomycin (SM)	5	0.7	1	2.8		0.9
MONORESISTANCE	**9**	**1.3**	**2**	**5.6**		**1.6**
Isoniazid (INH)	9	1.3	2	5.6		1.6
Rifampicin (RMP)	0	0.0	0	0.0		0.0
Ethambutol (EMB)	0	0.0	0	0.0		0.0
Streptomycin (SM)	0	0.0	0	0.0		0.0
MULTIDRUG RESISTANCE	**13**	**1.9**	**3**	**8.3**		**2.4**
INH + RMP	8	1.2	2	5.6		1.5
INH + RMP + EMB	0	0.0	0	0.0		0.0
INH + RMP + SM	1	0.1	1	2.8		0.3
INH + RMP + EMB + SM	4	0.6	0	0.0		0.5
OTHER PATTERNS	**0**	**0.0**	**0**	**0.0**		**0.0**
INH + EMB	0	0.0	0	0.0		0.0
INH + SM	0	0.0	0	0.0		0.0
INH + EMB + SM	0	0.0	0	0.0		0.0
RMP + EMB	0	0.0	0	0.0		0.0
RMP + SM	0	0.0	0	0.0		0.0
RMP + EMB + SM	0	0.0	0	0.0		0.0
EMB + SM	0	0.0	0	0.0		0.0
NUMBER OF DRUGS RESISTANT TO:						
0	654	96.7	31	86.1		96.0
1	9	1.3	2	5.6		1.6
2	8	1.2	2	5.6		1.5
3	1	0.1	1	2.8		0.3
4	**4**	**0.6**	**0**	**0.0**		**0.5**

*** Combined estimates were calculated from primary and acquired drug resistance but weighted by the proportion of retreatment cases in the NTP (see opposite page).**

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